Cancer Letters 535 (2022) 215620

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Natural killer cell therapy: A new frontier for obesity-associated cancer

Eimear Mylod [a], Joanne Lysaght [a], Melissa J. Conroy [a,b,*]

[a] Cancer Immunology and Immunotherapy Group, Department of Surgery, Trinity Translational Medicine Institute and Trinity St. James's Cancer Institute, St. James's Hospital, Trinity College Dublin, Dublin, 8, Ireland

[b] Cancer Immunology Research Group, Department of Physiology, School of Medicine, Trinity College Dublin, Dublin, 2, Ireland

ARTICLE INFO

Keywords:
Natural killer cells
Obesity
Immunotherapy
Obesity-associated cancer

ABSTRACT

Natural killer (NK) cell infiltration of solid tumours is associated with better outcomes, placing augmentation of NK cell abundance in tumours as an attractive immunotherapeutic approach. The unique ability of NK cells to target cancer cells without antigen specificity increases their versatility and applicability as an immunotherapeutic tool. However, successful utilisation of NK cell-based therapies in solid tumours is still at an early stage.

Obesity has become a global health epidemic, and the prevalence of obesity-associated cancers has significantly increased. Obesity-associated malignancies provide a unique challenge for the successful application of cell-based immunotherapies including NK cell-based therapies because significant numbers of NK and T cells are recruited to the visceral adipose tissue at the expense of successful tumour infiltration and eradication. As such, immunotherapy efficacy has been disappointing for obesity-associated malignancies such as oesophageal and gastric adenocarcinoma. Therefore, immunotherapies for obesity-associated cancers warrant our further attention. Indeed, it is becoming ever more obvious that more innovative approaches are needed to re-invigorate anti-tumour immunity and overcome immune exclusion in such tumours.

In this review, we briefly summarise the dysfunctionality of NK cells in obesity-associated cancer. We outline the NK cell-based immunotherapeutic approaches which hold promise as effective treatments in this disease space, including CAR-NK cells. Furthermore, we suggest future avenues which possess the potential to transform immunotherapy and specifically NK cell therapy efficacy for obesity-associated cancer.

1. Introduction

Amid a serious global obesity epidemic which results in ~4.5 million annual deaths, there is compelling epidemiological evidence linking obesity and the development of numerous cancers including colon, rectal, oesophageal, stomach, kidney, pancreas, liver, breast, ovary and endometrial [1–3]. Owing to escalating obesity rates, the prevalence of these obesity-associated cancers is expected to soar in the coming decades and it is predicted obesity will surpass smoking as the leading cause of preventable cancer within 20 years [4]. These obesity-associated cancers are coupled with poor 5-year survival rates at present, including 32% for gastric cancer, 20% for oesophageal and liver and a dismal 10% for pancreatic [5–8] (Table 1). It is evident that the growing rates of obesity in tandem with abysmal survival rates will lead to worsening outcomes for obesity-associated cancer patients. As such, this ever-growing group of cancer patients face meagre survival rates and urgently require new therapeutic options.

A so-called 'hot' tumour is immunologically enriched with a significant anti-tumour immune cell infiltrate, whilst a 'cold' or immune-excluded tumour is devoid of such anti-tumour immune cell infiltration. Cold tumours are instead enriched with suppressive regulatory T cells and myeloid-derived suppressor cells (MDSC) [9]. The overarching goal of cancer immunotherapy is to turn 'cold' tumours 'hot', to promote antigen presentation, augment T and natural killer (NK) cell activation and ultimately enhance tumour eradication [9]. Whilst immunotherapies have been heralded as a game changer for some poor prognosis cancers, immune checkpoint efficacy in obesity-associated malignancies have been disappointing. For example, efficacy in gastric cancer stands at 22% and oesophageal cancer at 15%, meaning there is still a large population of patients who do not gain clinical benefit from currently available immunotherapies [10,11].

We and others have reported poor infiltration of NK cells into the solid obesity-associated tumour, indeed in the case of oesophageal adenocarcinoma infiltration of NK cells into the tumour is lowest in the most viscerally obese patients [12–15]. NK cell infiltration of solid tumours is associated with better outcomes and therefore augmenting the

* Corresponding author. Cancer Immunology Research Group, Department of Physiology, School of Medicine, Trinity College Dublin, Dublin, 2, Ireland.
E-mail address: meconroy@tcd.ie (M.J. Conroy).

https://doi.org/10.1016/j.canlet.2022.215620
Received 9 December 2021; Received in revised form 16 February 2022; Accepted 3 March 2022
Available online 10 March 2022

Table 1
Relative risk of cancer at highest BMI category vs. normal BMI and associated survival rates. Relative risk data from a meta-analysis reported by the International Agency for Research on Cancer (IARC) working group [1]. 5-year survival rate data from cancer.net.

Cancer type or site	Relative risk of the highest BMI category versus normal BMI (95% CI)	5-year survival rate
Corpus uteri (endometrium)	7.1 (6.3–8.1)	81%
Oesophageal adenocarcinoma	4.8 (3.0–7.7)	20%
Liver	1.8 (1.6–2.1)	20%
Gastric cardia	1.8 (1.3–2.5)	32%
Kidney	1.8 (1.7–1.9)	75%
Pancreas	1.5 (1.2–1.8)	10%
Multiple Myeloma	1.5 (1.2–2.0)	54%
Meningioma	1.5 (1.3–1.8)	66%
Gallbladder	1.3 (1.2–1.4)	19%
Colon and rectum	1.3 (1.3–1.4)	65%
Ovary	1.1 (1.1–1.2)	49%
Breast (post-menopausal)	1.1 (1.1–1.2)	90%
Thyroid	1.1 (1.0–1.1)	98%

hindered NK cell infiltration of obesity-associated cancers is an attractive immunotherapeutic approach to help re-invigorate the immune response [16–19].

NK cells are central to tumour immunosurveillance, and their dysfunction has now been reported in several obesity-associated malignancies, placing them as a therapeutic candidate in this space. In this review, we present what is known about NK cell function and dysfunction in obesity and obesity-associated cancers. We explore the current NK cell-based immunotherapies that are under investigation, both preclinically and clinically. Additionally, we outline potential future avenues to explore in the sphere of NK cell-based therapies and discuss the challenges presented by obesity-associated cancer.

2. NK cells in the solid tumour

NK cells are innate immune cells with potent cytotoxic and cytokine-producing capabilities, and play a central role in cancer immunosurveillance, such that low cytotoxic activity is associated with increased cancer risk in humans [20,21].

2.1. NK cell biology

NK cells can be broadly categorised into two subsets with unique maturation status and functional specificities; $CD56^{bright}CD16^{dim}$ account for ~10% of circulating NK cells, produce the majority of NK cell-derived cytokines, and have little cytotoxic ability [20]. They express the chemokine receptors CCR7, CCR5 and CXCR3, and high levels of maturation marker CD27 [20,22,23] (Fig. 1). In contrast, the $CD56^{dim}CD16^{bright}$ subset predominate in the circulation, produce modest levels of cytokines and are highly cytotoxic, exhibiting greater levels of antibody-dependent cellular cytotoxicity (ADCC) [20,22]. The $CD56^{dim}CD16^{bright}$ circulating subset express high levels of CXCR1, CX3CR1 and CXCR4 and low levels of CD27 [23] (Fig. 1).

NK cell recognition and killing of target cells is controlled through a balance of activating and inhibiting signals (Fig. 1). NK cell inhibitory and activating receptor expression patterns are diverse among NK cells and allow for recognition of minute changes in ligand expression [24]. Synergistic signals from combinations of receptors are integrated to activate NK cell functions [24]. NK cell receptors include the killer immunoglobulin receptor (KIR) family, the c-type lectin family CD94-NKG2, including activating receptor NKG2D and inhibitory receptor NKG2A and the natural cytotoxicity receptors; NKp30, NKp44 and NKp46 [24] (Fig. 1). NK cells also mediate their cytotoxicity via the death receptor ligands TNF-related apoptosis-inducing ligand (TRAIL) and FasL [25]. Importantly, NK cells express immune checkpoint proteins programmed cell death protein 1 (PD-1) and T cell immunoreceptor with Ig and ITIM domains (TIGIT) which negatively regulate

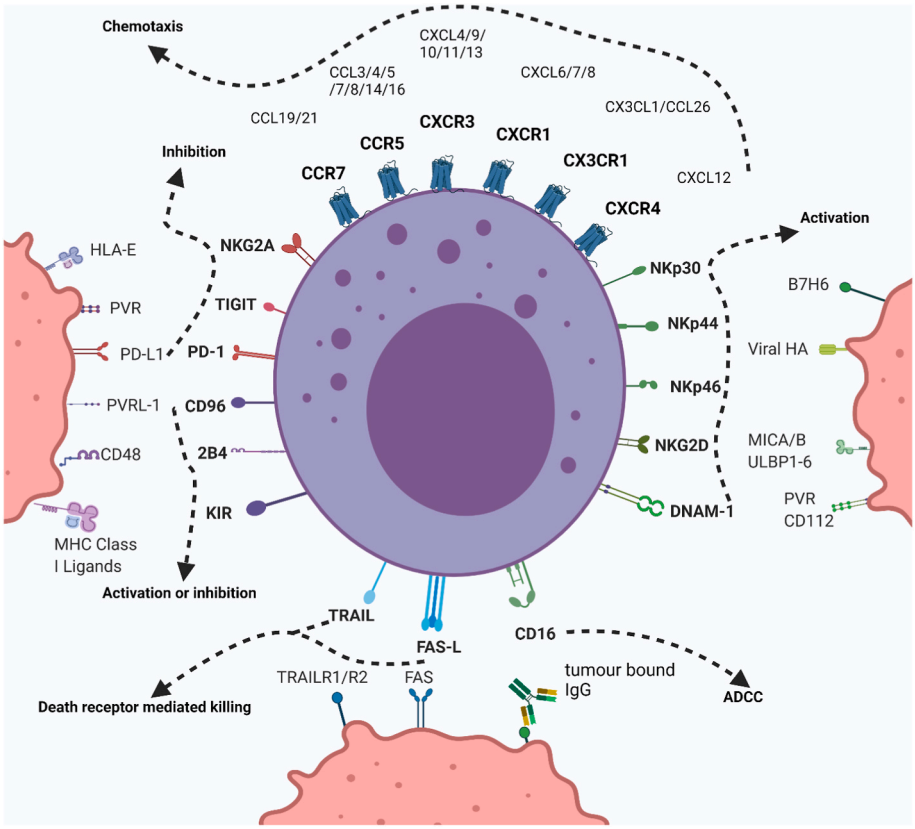

Fig. 1. ***NK Cell Receptors and Ligands***. NK cell activation is regulated by a complex network of activating receptors (green) and inhibitory receptors (red) or dual activating and inhibitory receptors (purple). Cognate ligands are expressed on the tumour cell. Loss of inhibitory signals or promotion of activating signals triggers NK cell activation, driving effector functions, including death receptor signalling via TRAIL and FasL (blue). CD16 mediates ADCC. Chemokine receptors on the surface of NK cells facilitate chemotaxis toward their cognate ligands. Created with BioRender.com.

their function and are common immunotherapeutic targets [26,27] (Fig. 1). CD56^{dim} NK cells also mediate their cytolytic effects via the activating receptor FcγRIIa (CD16) that binds the Fc portion of immunoglobulin (Ig) G to facilitate ADCC [27] (Fig. 1). Binding of CD16 to IgG leads to NK cell activation and induction of tumour cell death via cytotoxic granule release, inflammatory cytokine production and death receptor signalling [27].

NK cells have further functions beyond cytotoxicity and are important activators of the adaptive immune response. They produce numerous anti-tumour cytokines upon activation, such as IFN-γ which promotes downstream T cell responses and drives a Th1 immune response [20,28,29]. The diverse interactions of dendritic cells (DC) and NK cells in the tumour microenvironment (TME) is crucial in producing a robust immune response. DC derived chemokines recruit NK cells and CD8$^+$ T cells to the solid tumour, and likewise NK cell derived chemokines and growth factors recruit DC, potentially allowing them to localise in close proximity to facilitate NK-DC interplay [30–32]. NK cell derived cytokines TNF-α and IFN-γ induce the activation and maturation of DC [33]. In turn, DC derived IL-12 and IL-15 can activate NK cells [34]. DC can engulf antigens from tumour cells lysed by NK cells and present them on MHC class I molecules to CD8$^+$ T cells, inducing a robust adaptive immune response [20,29,35]. This cross-presentation is dependent on NK cell-mediated activation of DC [36].

2.2. The challenge of the solid tumour for NK cells

The harsh TME of solid tumours often presents an overall immunosuppressive microenvironment known to impair NK cell function [37]. Even if NK cells can successfully traffic to and infiltrate the solid tumour, they are met with a hostile environment which is primed to dampen and dysregulate their functionality.

Tumour cell NK cell receptor ligand shedding facilitates the interaction of soluble ligands with receptor bearing NK cells, resulting in defective expression of activating receptors and thus allows tumour cells to evade NK cell-mediated immune surveillance [38,39]. The phenomenon of tumour immunoediting also contributes to such immune suppression by favouring the selection of tumour cells with altered inhibitory or activating NK cell receptor ligand expression, thus developing resistance to NK cell-mediated attempts at tumour cell killing [40,41] (Fig. 2). In ovarian cancer, MUC16 expressing tumour cells are spared from NK cell mediated cytotoxicity and interfere with the formation of the immunological synapse which is required for NK cells to carry out their function [42].

The tumour-derived cytokine TGF-β can downregulate expression of activating receptors NKp30 and NKG2D on the surface of NK cells [43,44]. In turn, TGF-β can limit the cytotoxic capacity and IFN-γ production of NK cells and convert NK cells to their less cytotoxic type 1 innate lymphoid cell (ILC) counterparts [45–47] (Fig. 2). TGF-β has been shown to have detrimental effects on NK cell metabolism, inhibiting cytokine induced activation of mammalian target of rapamycin (mTOR), a known regulator of NK cell metabolism [48]. Glycolysis is crucial for NK cell effector function and TGF-β has been shown to inhibit this metabolic pathway via its induction of FBP1 [49]. In metastatic breast cancer patients, the TGF-β sequestering receptor Glycoprotein-A repetitions predominant (GARP) is overexpressed on NK cells from some patients, suggesting NK cells may contribute to their own dysfunction in cancer and highlighting GARP as a key mediator of this dysfunction [50]. The importance of metabolism in NK cell function has come to the fore in recent years. Indeed, metabolic changes are integral to NK cell effector functions including the production of IFN-γ and granzyme B [51,52]. In the TME, harsh physiological conditions caused by shortages of key nutrients, an overabundance of lipids, the acidic pH and the presence of tumour derived metabolites such as lactic acid can detrimentally affect NK cell metabolism and dampen NK cell mediated responses [53–56].

The unique chemokine signature of a tumour plays a central role in the recruitment of cell populations and thus the architecture of the TME [57,58] (Fig. 2). Tumour cells can alter the chemokine signature. In the setting of breast cancer TGF-β signalling can alter the chemokine signature of the tumour, thus dampening NK cell-mediated immunosurveillance of the tumour [59]. Recruitment of tumour-associated macrophages and MDSCs amongst other immunosuppressive cells is driven by chemokines, in particular CCL2 [60–62].

Physiological conditions such as hypoxia, a hallmark of the TME, exacerbate immune modulation of NK cells through a number of mechanisms, including diminished expression of key activating receptors in response to stimulation [63] and a reduction in IL-12 in a MDSC-dependent fashion, a key cytokine required for NK cell activation [64] (Fig. 2). NK cell anergy and a reduction of NKG2D expression ensue [65]. Hypoxia can also alter the chemokine signature leading to increased CCL28 release from solid tumours. This promotes the recruitment of immunosuppressive cells, such as Tregs, and dampens the recruitment of cytotoxic lymphocytes like NK cells [66,67] (Fig. 2). The overall acidic pH characteristic of the TME along with altered NK cell

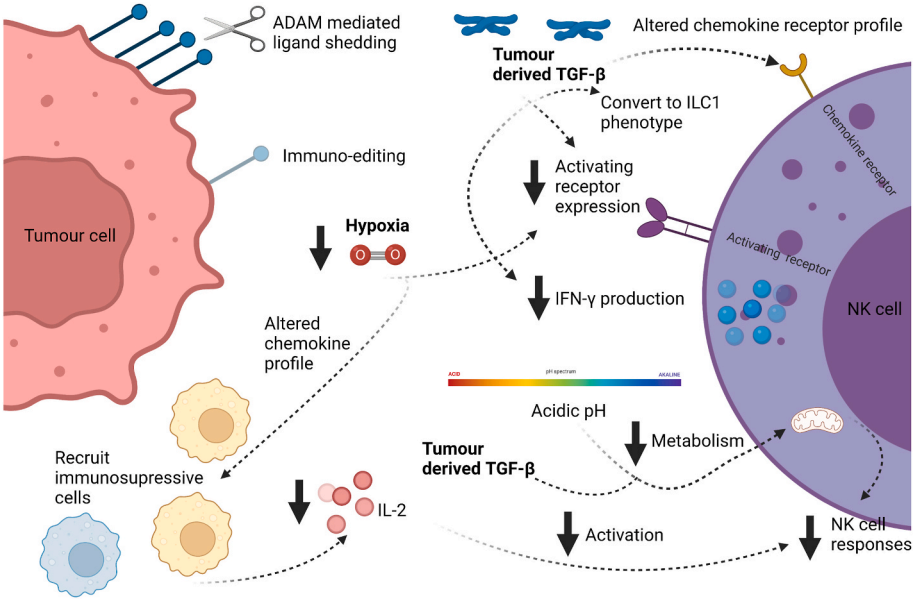

Fig. 2. ***NK cell dysfunction in the tumour microenvironment.*** Tumour-derived TGF-β can alter the chemokine and activating receptor profile of NK cells, affecting their phenotype and function. It can also decrease the production of IFN-γ and convert NK cells to an ILC1 phenotype. The hypoxic TME can alter IFN-γ production and the chemokine profile of the tumour, helping in the recruitment of immunosuppressive cells. These cells can dampen the IL-2 available, halting NK cell activation. The overall acidic pH in the TME and tumour-derived TGF-β can dampen NK cell metabolism which can dampen NK cell function. ADAM10 and ADAM17 in the TME can cleave NK cell activating receptor ligands from the surface of tumour cells. This along with immunoediting, the selection of tumour cells with decreased activating ligand expression can help to dampen NK cell activation. Created with BioRender.com.

metabolism due to lack of nutrient and oxygen availability, is also known to negatively impact NK cell functions including cytotoxicity and production of the cytokines TNF-α, IFN-γ and IL-10 [68–70].

3. NK cell dysfunction in obesity and obesity-associated cancer

The higher prevalence of tumours in obese cohorts has unearthed a link between obesity-driven inflammation and the hallmarks of cancer [71]. The development of obesity-associated cancer is dependent on multi-factorial changes in immune mediators, cytokines and adipokines. Obesity drives a state of chronic low-grade inflammation as a result of alterations in the endocrine function and secretory profile of the adipose tissue (AT) and associated immune cells, which is pro-tumorigenic [72]. Briefly, the systemic inflammation induced by obesity is believed to originate in the visceral adipose tissue (VAT), the largest compartment of which is the omentum. In lean VAT, a state of homeostasis is maintained by anti-inflammatory immune modulation, however expansion of VAT, coupled with the shift towards a more pro-inflammatory phenotype and accompanying adipose stress, drives immune cell accumulation in VAT and subsequent local and systemic inflammation [73]. Our group have reported that components of the anti-tumour immune response are severely dysregulated in patients with obesity-associated cancer [12,74–78].

3.1. NK cell dysfunction in obesity

3.1.1. Diminished NK cell activity in obese individuals

The dysfunctional state of NK cells in obesity is well established [79,80]. Analysis of so-called metabolically healthy and unhealthy obese patients revealed that chronic activation, as indicated by increased CD69 expression, is paralleled by increased inhibitory molecule expression in metabolically unhealthy obese individuals, ultimately culminating in lower NK cell cytotoxic activity [81,82] (Fig. 3). Circulating NK cells from obese adults and children similarly possess this chronically activated CD69^{+} phenotype [83,84]. Within the unique subsets of NK cells, there is an overall decrease in the CD56^{dim} subset in both obese adults and children, coupled with decreases in CD16 expression [83–85]. Circulating NK cell receptor profile alterations have been reported in obese cohorts, with reductions in the expression of the natural cytotoxicity receptor NKp46 [86], most apparent in subjects with the highest BMI [84]. Expression of death receptor ligand TRAIL and marker of degranulation CD107a is also diminished in obese cohorts [87]. NK cells from obese individuals exhibited dampened IFN-γ production, lower granzyme and perforin levels, and decreased cytotoxicity against tumour cell targets [54]. Obesity was marked by an accumulation of lipid droplets within NK cells, an indicator of a shift to lipid based metabolic pathways in response to the lipid rich environment characteristic of obesity [54]. This lipid uptake hampered NK cell cytotoxic capacity and restricted metabolic functions, further linking metabolic activity with NK cell cytotoxic abilities [54]. Overall, the shift in phenotype is likely to result in diminished cytotoxic activity of NK cells from obese cohorts against target cells [86,88] (Fig. 3). In the VAT depot of obese individuals, the surface receptor repertoire and activation status of NK cells is altered, with frequencies of KIR^{+}, NKG2D^{+}, NKp46^{+} and CD27^{+} NK cells significantly higher in the VAT compared to the periphery [89]. Hildreth et al. reported that mature NK cells are diminished in the AT of obese patients compared to their lean counterparts, with this decrease negatively correlating with BMI. Indeed, immature and tissue resident NK cell frequencies increased, probably due to this depletion of the mature subset [90]. It is of note that in the obese liver an ILC1-like phenotype of NK cells has been reported compared to lean livers [91]. This hints to the conversion of NK cells to their less cytotoxic ILC1 counterparts in the obese liver and may explain the altered phenotype seen in obese cohorts. Conversion of NK cells to ILC1 cells mediated by TGF-β has been touted as a mechanism by which tumours can evade NK cell recognition [45]. Further studies which differentiate between NK cells and ILC1 are warranted to accurately decipher this.

3.1.2. Role of NK cell responses in VAT inflammation in obesity

Several studies report the distinct obesity-associated phenotypes of NK cells within the VAT depot, believed to form a crucial link between obesity-induced adipose stress and VAT inflammation [89,92–95]. In a mouse model of obesity, NK cell activating ligands are upregulated on adipocytes within the VAT [92]. This results in increased NK cell activation and subsequent IFN-γ production, which mediates macrophage polarisation toward a pro-inflammatory phenotype, and potentiates systemic, body-wide inflammation [92]. Interestingly, macrophage infiltration of VAT and VAT inflammation could be attenuated by NK cell ablation [93,95]. Indeed, O'Sullivan et al. have shown that adipose resident NK cells are made up of both immature and mature NK cells and ILC1. In obesity, adipose derived IL-12 potentiated the accumulation of

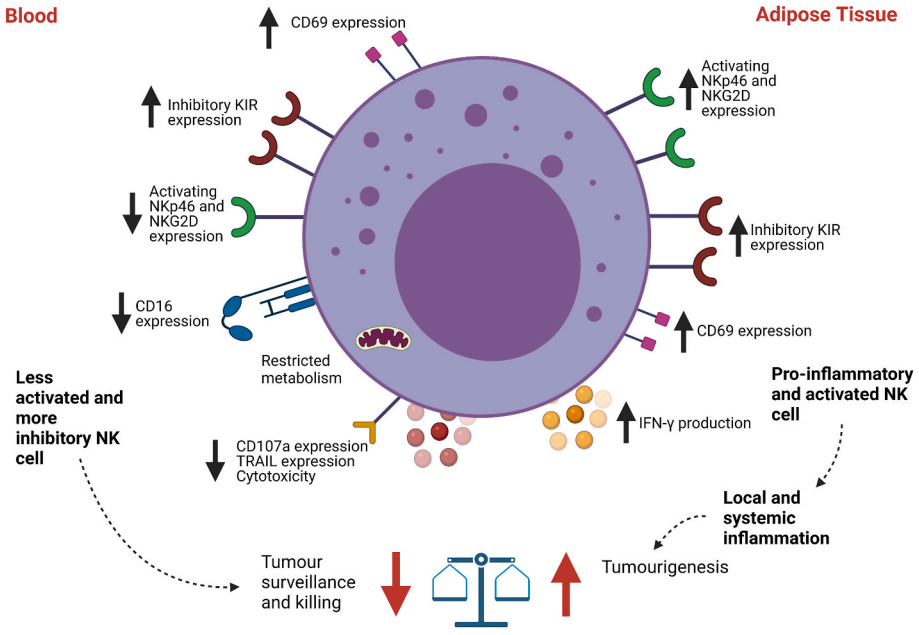

Fig. 3. ***NK Cell Dysfunction in Obesity: Inhibitory NK cell phenotypes in the circulation and pro-inflammatory NK cell profiles in the adipose tissue promote tumourigenesis and reduce tumour surveillance.*** Overview of obesity mediated NK cell dysfunctionality in the circulation (left) and adipose tissue (right). In the circulation expression of inhibitory KIR receptors is increased, while activating NKp46 and NKG2D receptor expression is decreased. NK Cell ability to degranulate along with cytotoxicity are decreased. Expression of the activating marker CD69 is increased, indicative of chronic activation. Metabolic activity is restricted. In the adipose tissue activating NKp46 and NKG2D receptor expression is increased along with inhibitory KIR expression. CD69 expression and IFN-γ production are increased, driving M1 macrophage polarisation. In the circulation this leads to a less activated and more inhibitory NK cell which can tip the balance in favour of decreased tumour surveillance and killing. In the adipose tissue a pro-inflammatory and activated NK cell phenotype is reported which contributes to local and systemic inflammation which can drive tumourigenesis. Created with BioRender.com.

ILC1 within adipose tissue, which along with tissue resident NK cells produce IFN-γ that drives M1 macrophage polarisation and inflammation with the VAT [90,96]. In obese subjects, the frequency of NK cells was higher in the VAT compared to their lean counterparts and this was coupled with heightened M1 macrophage polarisation in this compartment, further suggesting a role for NK cells in bolstering inflammation within the VAT [97]. Levels of the immune regulatory adipokine leptin are known to be increased in obese VAT [98]. Whilst short term leptin exposure increases cytokine production and cytotoxic capacity of NK cells, longer term exposure dampens NK cell cytotoxic effects and impairs proliferation [99]. This suggests a link between the elevated leptin levels in obesity, diminished NK cell effector functions and the potential negative implications for tumour immunosurveillance in obesity-associated cancer [99].

Overall, there is evidence which suggests that a shift away from a cytotoxic NK cell phenotype in obesity may hamper immune surveillance and pre-dispose such individuals to the development of cancer. Furthermore, a central role for VAT NK cells in pathological systemic inflammation in obesity has also been shown, thus suggesting that they might contribute to tumour-fuelling inflammation at the pre-malignant stage.

3.2. NK cell dysfunction in obesity-associated cancer

As integral players in anti-tumour immunity, NK cell impairment in obesity provides fertile ground for malignant growth and there are emerging reports of how this might be exploited with therapeutic intent in the escalating numbers of obesity-associated cancer patients.

3.2.1. Oesophageal cancer

In oesophageal adenocarcinoma (OAC), NK cell frequencies are most diminished in the tumour of the most viscerally obese patients [12]. Our group has identified the active recruitment of NK cells to the soluble chemotactic cues of the omentum in OAC [77]. Furthermore, within the omentum there are significantly lower frequencies of NK cells and our reported data strongly indicate that this is a result of enhanced levels of NK cell apoptosis within this inflamed tissue [12,77]. This suggests NK cells migrate preferentially to the omentum at the expense of successful infiltration of the tumour [12,77]. Indeed exposure to the soluble chemotactic cues of the omentum can paralyse subsequent NK cell migration to the tumour [100]. Within the omentum of OAC patients, there are reductions in $NKp46^+$ and TNF-α producing NK cells, and an increase in $CD27^+$ and IL-10 producing NK cells, thus strengthening the notion of a less cytotoxic NK cell phenotype in obesity-associated cancer [12,77]. This is solidified by the significantly lower frequencies of TRAIL and $FasL^+$ NK cells in the circulation and omentum of obese OAC patients compared to their lean counterparts [100].

3.2.2. Colorectal cancer

Colon cancer is another exemplar model of inflammation-driven and obesity-associated cancer. In animal models of diet-induced colon cancer, frequencies of intratumoural NK cells are decreased compared to lean counterparts and NK cell migration to the tumour is impaired during early tumour development, resulting in decreased NK cell frequencies within the tumour [101,102]. Such diminished NK cell numbers are not limited to tumour with reduced frequencies of circulating and AT NK cells in both obese colorectal cancer patients and in an animal model [101,103]. In consequence and unsurprisingly so, colon tumour size, weight and quantity is increased in obese rats compared to their lean counterparts [101,103]. The phenotype of NK cells was also altered, with splenic NK cells expressing significantly less NKG2D and NKp46 [101,103].

3.2.3. Endometrial cancer

Endometrial cancer has the highest association of any cancer with obesity [1]. In the TME of endometrial cancer, tumour resident NK cells expressed higher levels of immune checkpoint TIGIT and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) compared to NK cells recruited to the tissue from the circulation, with expression of these inhibitory molecules increasing with disease severity [104]. TIGIT acts as an immune checkpoint and thus mediates exhaustion of these cells in tumours and suppresses NK cell cytotoxicity and IFN-γ production upon interaction with its ligands PVR and PVRL2 [105–107]. Profiling of the TME revealed significantly lower levels of chemokines CCL27, CCL21 and CXCL12 and higher levels of the cytokines IL-6 and IL-1β [104]. CCL27, CXCL12 and CCL21 are known NK cell chemoattractants. Thus, reduced production of these chemokines from the endometrial TME may result in decreased recruitment of NK cells to the tumour, and as such acts as an immunosuppressive mechanism utilised by the tumour. A dual role for both IL-6 and IL-1β has been suggested in recent reports, with both driving tumour progression. Indeed IL-6 can negatively regulate NK cell cytotoxicity. This suggests the endometrial TME profile may reduce NK cell function and recruitment to the tumour site [104]. A recent study from Dyck et al. suggests a higher BMI is associated with a cold tumour phenotype in endometrial cancer and characterised by a low infiltration of effector T cells [108].

3.2.4. Breast cancer

Several studies established that breast tumour size and quantity, along with metastases were greater in obese animals compared to their lean counterparts [109–111]. Lower frequencies of circulating NK cells in an obese breast cancer model suggest a role for NK cells in controlling tumour growth and metastasis [110]. Furthermore, NK cells had reduced activating receptor NKp46 expression and impaired cytotoxicity in obese breast cancer models compared to their lean counterparts [109,110,112]. In fact, the circulating NK cells of patients with metastatic breast cancer exhibit reduced TRAIL expression and cytotoxicity, coupled with impaired IFN-γ production [50].

The overwhelming evidence from studies in cancer patients and models is that NK cells are less cytotoxic in obesity-associated cancer. Therefore NK cell therapies would be an ideal therapeutic option to replenish numbers and enhance NK cell-mediated immune responses. The efficacy of the next generation of NK cell therapies for obesity-associated cancer will be determined by the innovations used to overcome the challenges in these patients.

4. Targeting obesity-associated cancer using NK cell-based approaches – current state of the field

Here we review current NK cell-based immunotherapeutic approaches in both the pre-clinical and clinical trial settings. The clonal NK cell line NK-92 is currently the lead candidate for NK cell-based immunotherapeutic approaches, with over 30 registered trials on clinicaltrials.gov. However, engineered cells are emerging as a promising strategy that may aid in overcoming the deleterious effects of the TME and improve NK cell homing to the tumour.

4.1. Adoptive NK cell immunotherapy

Owing to the often-dysfunctional immune system in cancer patients, adoptive transfer of immune cells to supplement the existing repertoire is an appealing immunotherapeutic approach. The applicability of cellular based immunotherapies for solid tumours such as Chimeric antigen receptor (CAR) T cell therapies have been successful in haematological malignancies but have been hampered by the requirement for cells to be generated from a patient's own immune cells. This limits their scalability and applicability compared to other immunotherapies [113]. CAR-T cells are also limited by the potential risk for GVHD if using an allogenic T cell. Subsequent development of cytokine release syndrome, a potentially fatal side effect, can develop as a result of off-target effects of the CAR-T cell product [114]. However, one of the most significant hurdles in the development of CAR-T cell therapies is

the reliance on generating them from a patient's own blood which can delay cell retrieval. Often already impaired T cell frequencies and functions are further impacted by first-line treatments [114]. NK cell therapies hold great promise and could even surpass T cell therapies for reasons owed to their intrinsic biology and function, giving them the potential to become a truly *off-the-shelf* therapeutic option [115] (Fig. 4) (Table 2).

Clonal NK cell lines present an auspicious solution to NK cell dysfunction in cancer and multiple clinical trials are utilising either NK-92 cells or KHYG-1 cells as a readily available source of NK cells for *off-the-shelf* therapies. NK-92 offer a range of benefits for use as an NK cell therapy; they are maintained well *in vitro,* are highly cytotoxic and can be easily genetically modified to recognise tumour antigens or upregulate activating receptors [116,117]. NK-92 express numerous activating receptors including NKG2D, NKp30, NKp46 and 2B4 [117]. However, NK cell lines do present their own challenges including the requirement for irradiation prior to infusion which prevents *in vivo* proliferation as these cells do have malignant origins [118]. As such, this can lead to the requirement for multiple infusions for patients which bring challenges both logistically and financially. This is in stark contrast to CAR-T cell therapies which have proven persistence and efficacy 10 years post-treatment [113]. Alternative sources of NK cell therapies include peripheral blood, cord blood or induced pluripotent stem cells (iPSC). Peripheral blood NK cells are phenotypically and functionally mature and mostly comprised of $CD56^{dim}$ cytotoxic populations compared to cells isolated from cord blood or derived from iPSC. Both cord blood and iPSC derived NK cells have high proliferative capacities and are amenable to cytokine stimulation to shape their phenotypes [114].

First in human trials show NK-92 to be safe after numerous infusions and feasible for use and they currently represent the most frequent source of NK cells currently in trial. Results using unmodified NK-92 cells demonstrated safety and some efficacy in haematological malignancies and an assortment of solid malignancies, including colorectal cancer [119–122]. However, the next generation of NK cell therapies armed with CARs specific to tumour-associated antigens, activating receptors or signalling molecules hold the potential to boost NK-92 efficacy. CARs are recombinant antigen receptors which upon binding to cognate ligands on target cells can modulate effector lymphocyte activity, resulting in immune cell activation and survival [123]. Both human primary NK cells and NK cell lines may represent superior CAR drivers to T cells due to perceived advantages possessed by NK cells, including superior production efficiency and the potential for enhanced killing activity in light of NK cells ability to kill tumour cells irrespective of MHC status and without prior activation [124].

4.1.1. *Tumour-specific antigen CARs*

In an orthotopic model of pancreatic cancer, CAR-NK cells against the tumour antigen ROBO1 markedly reduced tumour growth [125]. In a case report, treatment of a pancreatic cancer patient with liver involvement with ROBO1 CAR-NK cells lead to stable disease for 5 months and an overall survival of 8 months [126]. As such, trials employing these CAR-NK cells in pancreatic and other solid tumours are ongoing (NCT03941457, NCT03931720, NCT03940820) (Table 2). In a pulmonary metastasis model of liver cancer, treatment with HER2 CAR-NK-92 cells reduced the frequency of lung tumour nodules [127]. HER2 CAR-NK-92 cells lysed HER2 expressing tumour cells *in vitro* that were resistant to killing by the parental NK-92 cells [127]. Importantly, in an *in vivo* orthotopic breast cancer model, HER2 CAR-NK-92 function was retained and cells were enriched in the tumour [127]. In a HER2 expressing xenograft brain metastasis model of breast cancer, HER2 CAR-NK-92 cells were successfully delivered across the blood brain barrier using focused ultrasound, resulting in functional cells within the tumour which retained cytotoxic capacity against their target cells [128]. HER2 CAR-NK-92 cells lysed $HER2^{+}$ gastric cancer cells, accompanied by increased levels of IFN-γ and TNF-α production. *In vivo* HER2 CAR-NK-92 cells successfully eliminated small gastric tumour xenografts; however larger tumour xenografts were not contained [129]. Glypican 3 (GPC3) is highly expressed in the liver and undetectable in normal tissue, making it an ideal target in hepatocellular carcinoma immunotherapy [130]. CAR-NK-92 against GPC3 had potent and specific anti-tumour activities *in vitro* and *in vivo* in a mouse model of hepatocellular carcinoma [130]. NK-92 CARs targeting CD147, another target highly expressed in the liver, have been shown to kill hepatocellular carcinoma cells *in vitro*, and halt progression of hepatocellular carcinoma in both xenograft and PDX murine models [131]. Sahm et al. created a CAR-NK-92 cell with ectopic expression of IL-15 and the targeting effects of EpCAM. This CAR-NK-92 cell therapy could proliferate without the need for exogenous IL-15 and possessed highly selective killing against EpCAM-expressing breast carcinoma cells *in vitro*, compared to their parental NK-92 counterparts [132]. EpCAM

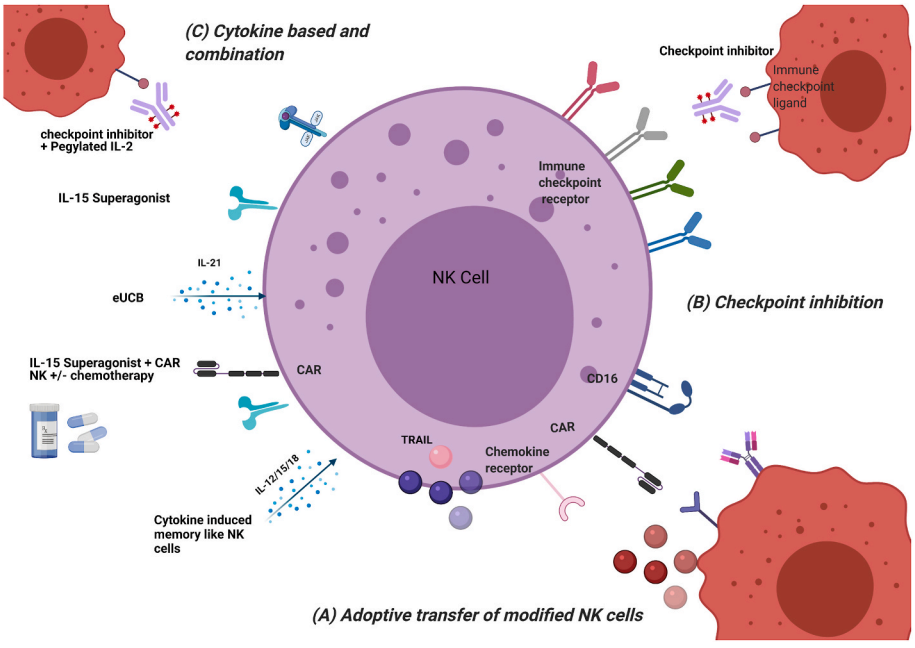

Fig. 4. ***Potential NK cell immunotherapeutic approaches for obesity-associated cancer***. (A) Adoptive transfer of modified or unmodified primary NK cells or NK cell lines. Modification to express the CD16 receptor, chemokine receptors or chimeric antigen receptors against a host of tumour antigens. (B) Inhibition of NK cell immune checkpoints by utilising antibodies against the specific chemokine ligand expressed on the tumour cells or within the tumour microenvironment. (C) Utilising IL-15 super-agonists alone or in combination with CAR NK cells and/or chemotherapy. Pegylated IL-2 alone or in combination with immune checkpoint inhibitors. Generation of cytokine induced memory-like NK cells using IL-12, IL-15 and IL-18. Pre-activation and expansion of NK cells using IL-21. Created with BioRender.com.

Table 2
CAR-NK cell approaches *in vitro*, *in vivo* and in clinical trial. OS; Overall survival, PB; Peripheral blood, SD; Stable disease.

Target	Cell source	Cancer type	*In vitro*	*In vivo*	Clinical trial results	Ongoing Trials	Phase	Reference
Tumour Specific								
ROBO1	Not specified	Pancreatic		Reduced tumour growth	SD 5 months OS 8 months	NCT03941457	1/2	[125, 126]
HER2	NK-92	Liver associated lung metastasis	Lysed target cell	reduced lung nodule frequency				[127]
HER2	NK-92	Breast		CAR-NK cells enriched in tumour				[127]
HER2	NK-92	Breast associated brain metastasis		Functional cells within the tumour Cytotoxicity against target cells				[128]
HER2	NK-92	Gastric	Lysed target cell Increased IFN-γ and TNF-α production	Eliminated small tumours				[129]
GPC3	NK-92	Liver	Lysed target cells Increased IFN-γ production	Enhanced tumour infiltration Lysed $GPC3^{+}$ tumour cells				[130]
CD147	NK-92	Liver	Lysed target cells	Controlled tumour growth				[131]
EpCAM	NK-92	Colorectal	Lysed target cells	Infiltrated tumour Lysed tumour cells				[133]
EpCAM	NK-92	Breast		Lysed tumour cells				[132]
EGFR	PB	Breast associated brain metastasis	Lysed target cells Increased IFN-γ production					[134]
EGFR	NK-92	Breast associated brain metastasis	Lysed target cells Increased IFN-γ production	Lysed tumour cells				[134]
Tissue factor	NK-92	Breast		Lysed tumour cells				[135]
FOLR1	KHYG1	Gastric	Lysed target cells	Lysed tumour cells				[136]
BCMA	PB	Multiple Myeloma		Successful trafficking to tumour Poor disease control				[138]
BCMA	Cord blood	Multiple Myeloma				NCT05008536 NCT03940833	1 1/2	
High affinity $CD16^{+}$ NK cells								
PD-L1	NK-92	Gastric	Lysed target cells					[140]
PD-L1	NK-92	Colon	Lysed target cells					[140]
PD-L1	NK-92	Breast	Lysed target cells	Successful trafficking to tumour Delayed tumour growth				[140]
Activating and inhibitory receptors								
NKG2D	PB	Colorectal	Lysed target cells	Lysed tumour cells Delayed tumour growth Reduced tumour burden	2/3 patients reduced cancer cell frequency in ascites reduced ascites	NCT05213195	1	[141]
NKG2D	Pluripotent stem cells	Ovarian	Lysed target cells	Lysed tumour cells Reduced tumour burden Prolonged survival				[142].
NKG2D	PB	Multiple Myeloma	Lysed target cells	Reduced disease burden 25% remained disease free				[143]
B7–H3	NK-92	Colorectal	Lysed target cells					[144]
Death Receptor Ligand								
TRAIL	NK-92	Colorectal	Secreted high levels of TRAIL Lysed target cells	Successful trafficking to tumour Inhibited tumour growth				[146]
Dual Targeting								
NKG2D TGF-β	NK-92	Liver	Resistant to TGF-β mediated suppressive signalling No NKG2D. downregulation	Lysed tumour cells Increased IFN-γ production inhibition Tregs differentiation				[147]
BCMA CD38	Induced pluripotent stem cells	Multiple Myeloma	Lysed target cells	Lysed tumour cells Synergised with daratumumab		NCT05182073	1	[149]

CAR-NK-92 cells can specially recognise and kill EpCAM-expressing colorectal cancer cells *in vitro* [133]. Furthermore, *in vivo* in an EpCAM-expressing xenograft mouse model, the CAR-NK cells could successfully home to tumour, where they had cytotoxic capacity against their target cell [133].

EGFR CAR-NK-92 cells and EGFR CAR-NK cells displayed superior cytotoxicity and cytokine production compared to their non-transduced counterparts *in vitro* against breast cancer cell lines. In a mouse model of breast cancer brain metastasis, EGFR CAR-NK-92 cells injected intratumorally resulted in reduced tumour growth compared to controls [134]. In triple negative breast cancer, antigen identification can prove more difficult. As such, Hu et al. employed tissue factor as a common yet selective antigen for triple negative breast cancer. Tissue factor-targeting CAR-NK cells were effective at killing breast carcinoma cells in both patient-derived and cell line-derived xenograft models [135].

In the upper GI space, folate receptor 1 (FOLR1)-targeting CAR-KHYG1 cells had strong cytotoxic effects against FOLR1-expressing gastric cancer cells *in vitro,* and in a xenograft model of gastric cancer [136]. The antigen 5T4 is highly expressed on tumour tissues and has restricted expression on normal cells, making it an ideal target [137]. A trial using anti-5T4 CAR-NK cells is ongoing in solid tumours (NCT05194709, NCT05137275). In a xenograft mouse model of multiple myeloma (MM), anti-BCMA CAR-NK cells successfully trafficked to the tumour, however disease control was poor [138]. A trial using anti-BCMA NK cells derived from cord blood in MM is ongoing (NCT05008536, NCT03940833).

4.1.2. High affinity CD16^{+} NK cells

NK-92 cells can be engineered to express the high affinity CD16, known as haNK cells, to facilitate ADCC and thus increase clinical efficacy [139]. High affinity NK cells armed with a CAR targeting the immune checkpoint ligand PD-L1 successfully lysed a number of human cancer cell lines, including gastric, colon and breast carcinoma. Furthermore, they preferentially lysed PD-L1^{high} instead of PD-L1^{low} human breast cancer cell lines *in vitro* [140]. The PD-L1 t-haNK successfully trafficked into PD-L1-expressing engrafted breast tumours *in vivo* and delayed tumour growth [140].

4.1.3. Activating and inhibitory ligand CARs

CAR-NK cells expressing the activating receptor NKG2D had significantly improved cytotoxic activity against colorectal carcinoma cell lines *in vitro* and *in vivo,* delayed tumour progression and decreased tumour burden in mouse models [141]. In a pilot clinical trial, autologous or allogenic NK cells were prepared and transduced with the NKG2D CAR construct. No serious adverse effects were reported and no GVHD was reported in those who received haploidentical NK cells [141]. Two of three patients with extensive metastatic colorectal cancer treated with infusion of NKG2D CAR-NK cells had a reduction in cancer cell frequency in the ascites fluid and an overall reduction in ascites. A third patient had tumour regression in the liver [141]. A phase 1 trial in metastatic colorectal cancer patients is ongoing (NCT05213195). NKG2D-expressing iPSC-derived NK cells displayed superior activity against ovarian cancer cells *in vitro* and *in vivo*, inhibiting growth and prolonging survival in an ovarian cancer xenograft model [142]. NKG2D CAR-NK cells exhibited greater cytotoxicity *in vitro* against MM target cells and importantly, showed minimal activity against healthy cells. *In vivo*, NKG2D CAR-NK cells mediated highly efficient halting of MM growth, with 25% of mice remaining disease free [143].

The inhibitory ligand B7–H3 is highly expressed on colorectal cancer cell lines. Thus, CAR-NK-92 cells against B7–H3 displayed enhanced activation, degranulation and cytotoxicity against B7–H3^{+} colorectal cancer cell lines compared to their parental counterparts [144].

4.1.4. Death receptor ligand TRAIL-NK cells

The death receptor ligand TRAIL is known to be involved in the cytotoxic activity of activated NK cells against TRAIL-sensitive tumour cells but importantly not normal cells making it a popular immunotherapeutic target [25,145]. To overcome the short half-life, Song et al. sought to design a secretory TRAIL-expressing NK cell-based therapy [146]. NK-92 cells were transduced with the extracellular domain of TRAIL. These cells could secrete high levels of TRAIL protein and induce apoptosis in colorectal cancer cell lines. Importantly, in a mouse model of colon cancer, these cells could infiltrate the tumour and inhibit tumour growth [146]. These TRAIL-secreting NK cells could help overcome obesity-associated impairments in the cytotoxicity of NK cells.

4.1.5. Dual target CARs

Wang et al. engineered NK-92 cells to express a CAR containing TGF-β type II and activating receptor NKG2D, to convert the suppressive signalling usually mediated by TGF-β into an activation signal [147]. These NK-92 were resistant to TGF-β mediated suppressive signalling and did not downregulate NKG2D. Enhanced cytotoxic ability and IFN-γ production in a mouse model of hepatocellular carcinoma were also reported. Interestingly, due to reduced levels of TGF-β within the tumour as a result of signalling through the TGF-β CAR-NK cells, there was also a significant inhibition of the differentiation of human naive CD4^{+} T cells to Tregs [147]. FT576 is an NK cell therapy engineered with 4 anti-tumour modalities including an anti-BCMA CAR, a non-cleavable version of CD16, an IL-15 receptor fusion protein and a CD38 knockout to prevent mAb mediated NK cell fratricide [148]. These alterations allow the NK cell to target both BCMA and CD38 as MM antigens [148]. FT576 NK cells had enhanced cytotoxicity against MM cell lines and enhanced ADCC when combined with the anti-CD38 mAb daratumumab [148]. In a xenograft mouse model of MM, FT576 displayed superior anti-tumour effects and was highly synergistic with daratumumab [149]. A trial in MM is ongoing (NCT05182073).

CAR-NK cells are still in the pre-clinical development and early phase trial stages for solid tumours, depending on the target of choice. In blood-based malignancies, positive results have been reported in early phase trials [150,151]. CAR-modified NK cells hold great potential in the realm of obesity-associated cancer and may be able to not only successfully drive NK cells to the solid tumour but concurrently boost their effector functions. The adoptive transfer of NK cells, be it allogenic primary NK cells or NK cell lines, presents the opportunity to overcome the functional impairment of the immune system in the obese cancer patient through the replacement and restoration of NK cell populations.

4.2. Immune checkpoints and inhibitory receptors

Inhibitory receptor and immune checkpoint signalling limits immune cell function, making blocking these pathways an attractive immunotherapeutic target [152]. A number of immune checkpoint inhibitors including pembrolizumab (*anti*-PD-1), nivolumab (*anti*-PD-1) and ipilimumab (*anti*-CTLA-4) have been approved in recent years for a host of cancers, including hepatocellular carcinoma, colorectal, and gastric cancer. In a small subset of patients in whom these treatments are effective, they have the potential to transform outcomes, however there is still a large proportion of patients who do not respond and optimal patient stratification approaches are under investigation [153]. Immune checkpoints are frequently shared between NK cells and T cells meaning targeting them will have wide ranging effects. NK cells can play a role in the therapeutic effects of immune checkpoint blockade [154] (Fig. 4). For instance, high PD-1 expression on peripheral and tumour-infiltrating NK cells from patients with gastrointestinal cancers has been reported, with a high expression indicating poor survival in oesophageal and liver cancers [155].

4.2.1. NKG2A

HLA-E, the ligand of inhibitory receptor NKG2A, is frequently overexpressed on tumour tissues, including pancreas, stomach, colon, and liver [156–158]. Furthermore tumour infiltrating NK cells frequently

express high levels of NKG2A in liver cancer and melanoma [156,157]. NKG2A expression is not limited to NK cells however, as $CD8^+$ T cells can also express this immune checkpoint [159]. NKG2A blockade enhances NK cell-mediated anti-tumour immunity *in vitro* and *in vivo* in a murine lymphoma model and development of NK cells lacking NKG2A evade HLA-E mediated immune mediation [156,160]. In patients with ovarian cancer, treatment with the *anti*-NKG2A mAb (monoclonal antibody) monalizumab was well tolerated and short-term disease stabilisation was observed [161]. HLA-E expression is more abundant than PD-L1 in numerous human cancers including lung, pancreas, stomach, colon, head and neck, and liver, making a combination of NKG2A and PD-1/PD-L1 blockade a therapeutic concept of interest [156]. Combination blockade in mice resulted in improved tumour control and synergistic NK cell dependent anti-tumour efficacy with improved survival compared with PD-1/PD-L1 blockade alone [156]. A trial combining *anti*-NKG2A mAb monalizumab and *anti*-PD-L1 mAb durvalumab in patients with solid tumours is currently ongoing (NCT02671435), with preliminary results in colorectal cancer showing promise, reporting 8% of patients had partial response and 28% had stable disease [162] (Table 3).

4.2.2. TIGIT

TIGIT is an immune checkpoint which mediates exhaustion of NK cells in the tumour, therefore targeting TIGIT is of therapeutic value to help alleviate NK cell exhaustion [105–107]. TIGIT blockade alleviated NK cell exhaustion, slows tumour growth in an NK cell dependent manner and enhances T cell-mediated anti-tumour responses *in vivo* [107]. TIGIT was highly expressed on tumour-infiltrating NK cells in colon cancer patients compared to those in the peritumoral region [107]. In a metastatic model of breast cancer, TIGIT was widely expressed on NK cells in the metastatic sites of the spleen, liver and lungs. Furthermore, a high frequency of $TIGIT^+$ tumour infiltrating NK cells was observed in mouse models of colon and breast cancer. Interestingly, the $TIGIT^+$ NK cells were primarily negative for the alternative immune checkpoints PD-1 and CTLA-4, suggesting that exhausted NK cells may not respond to therapies targeting these immune checkpoints [107]. The TIGIT-expressing NK cells in these breast and colon cancer models had reduced anti-tumour effector functionality, expressing less TRAIL, CD107a and NKG2D. Importantly, TIGIT deficiency both alleviated NK cell exhaustion and slowed tumour growth in mice [107]. *In vivo,* blockade of TIGIT prevented NK cell exhaustion in both colon and breast cancer mouse models, restoring tumour infiltrating NK cell degranulation and cytokine production. Overall, this suggests *anti*-TIGIT mAbs may help reverse NK cell exhaustion [107]. Trials exploring TIGIT monotherapy in solid tumours, including ovarian and colon cancer are ongoing (NCT03628677, NCT04353830, NCT04354246) (Table 3).

4.3. Cytokine based therapies

Enhancing NK cell activation has been central to the development of NK cell based immunotherapeutic strategies and cytokines are one of the most commonly used methods to boost NK cell activation *in vivo*. IL-15 is a vital NK cell cytokine which has generated considerable interest in the realm of NK cell-based immunotherapy as an alternative to using IL-2 [163]. IL-2 and IL-15 overlap in several key functions, including supporting the proliferation and activation of NK cells. IL-2 can support the persistence of regulatory T cells (Tregs), which is undesirable in the context of anti-tumour immunity [164,165]. IL-15 superagonists have gained considerable traction in recent years as a complement to other NK cell-based immunotherapies and to help support the persistence of NK cells [166].

In a xenograft gastric cancer mouse model, treatment with the fusion protein dsNKG2D-IL-15 enhanced NK cell infiltration into the tumour and treatment with this fusion was more effective than IL-15 alone in suppressing tumour growth [167]. The IL-15 superagonist, ALT-803 boosted NK cell cytotoxicity against ovarian cancer *in vitro* and *in vivo* [168]. ALT-803 supported the expansion of cytotoxic NK cell populations and boosted NK cell mediated anti-tumour effects in breast and colon cancer mouse models [169]. A trial using ALT-803 in ovarian cancer is ongoing (NCT03054909).

Combinations of IL-12, IL-15 and IL-18 to pre-activate NK cells for immunotherapy is an emerging strategy. These cells, known as cytokine induced memory-like (CIML) NK cells possess memory-like characteristics which allow for superior proliferation and persistence, along with enhanced cytokine production following re-stimulation [170,171]. In a xenograft mouse model of ovarian cancer CIML NK cells had enhanced IFN-γ production and superior killing of target cells, exhibiting an overall potent anti-tumour effect compared to naïve NK cells [172]. In the setting of MM a combination of CIML NK cells, IL-2 and the antibody redirecting molecule BHV-1100 which targets the common MM antigen CD38 is currently in trial (NCT04634435). Indeed, CIML NK cells may hold promise for CAR based NK cell therapies owing to their persistence and proliferation profiles along with their enhance anti-tumour effector functions. Of note, a study by Kedia-Mehta et al. reported impaired cytokine mediated training of NK cells from obese patients as a result of metabolic defects characteristic of obese NK cells [173]. This suggests harnessing autologous NK cells for CIML NK cell-based therapies for obese cancer patients may not be effective and that alternative sources of NK cells for the generation of CIML NK cells may be required in such cohorts.

Understandably, combination therapies exploring NK cell-based immunotherapies, immune checkpoint inhibitors, cytokine superagonists and traditional chemotherapy are of great interest. It is believed combining immunotherapies with traditional treatment modalities offers the potential for synergistic effects which may halt tumour progression and boost survival [174].

Monotherapy using pegylated IL-2 (NKTR-214) in a mixed population of pre-treated cancer patients including breast and colorectal cancer showed clinical activity including shrinkage of the tumour and stable disease. Furthermore, frequencies of peripheral NK cells increased following treatment [175]. Interestingly, the frequencies of $PD\text{-}1^+$ NK cells were also increased and NKTR-214 has been shown to synergise with checkpoint blockade therapies [176,177]. As such, a number of trials combining NKTR-214 with checkpoint blockade are underway

Table 3
Immune checkpoint-based therapies *in vivo* and in clinical trial. ICI; Immune checkpoint inhibitor, PR; Partial response SD; Stable disease.

Agent	Target	Cancer	*In vivo*	Clinical trial results	Ongoing trial	Phase	Reference
Monalizumab	NKG2A	Ovarian		Short term disease stabilisation			[161]
Monalizumab + Durvalumab	NKG2A ICI + PD-L1 ICI	Colorectal	Improved tumour control Synergistic NK cell dependent anti-tumour response	8% PR 28% SD	NCT02671435	1/2	[156, 162]
13G6	TIGIT	Colon and Breast	Restoration of tumour infiltrating NK cell degranulation and cytokine production				[107].
Domvanalimab	TIGIT	Solid tumour			NCT03628677	1	
IBI939	TIGIT	Solid tumour			NCT04353830	1	
COM902		Multiple Myeloma, Colon and Ovarian			NCT04354246	1	

(NCT03435640, NCT02869295). Initial results from a trial NKTR-214 in combination with the PD-1 immune checkpoint inhibitor nivolumab in a range of solid tumours including breast and colorectal cancer (NCT02983045) have been reported. This combination was well tolerated and 18.9% of patients had a complete response [178].

Umbilical cord blood derived NK cells expanded with IL-21 (eUCB) had superior cytotoxicity against colorectal cancer cell lines *in vitro* and produced high levels of IFN-γ and TNF-α compared to IL-2 stimulated cells [179]. In a HT29 xenograft model mouse model of colorectal cancer there was enhanced infiltration of eUCB NK cells into the tumour coupled with tumour shrinkage. However in the alternative LoVo colorectal tumour mouse model infiltration was poor and no significant tumour shrinkage was noted [179]. Combination of the anti-angiogenic bevacizumab with eUCB resulted in increased NK cell infiltration and significant tumour shrinkage compared to either treatment alone [179]. This suggests a combination of anti-angiogenic drugs with NK cell therapies may boost NK cell infiltration into the solid tumour and thus enhance efficacy. A trial combining bevacizumab and allogeneic NK therapy is investigating this combinational approach (NCT02857920).

In the setting of pancreatic cancer, the combination of low-dose chemotherapy, haNK cells, ALT-803, and an *anti*-PD-L1 mAb was examined in a heavily pre-treated patient group. 75% of patients had a best response of stable disease (≥8 weeks) and the median progression free survival was 7.1 months and median overall survival was 8.2

Table 4
Combination NK cell-based therapies *in vitro*, *in vivo* and in clinical trials. CD; Controlled disease, ICI; Immune checkpoint inhibitor, OS; Overall survival, PFS; Progression free survival, SD; Stable disease.

Agent	Target	Cancer	*In vitro*	*In vivo*	Clinical trial results	Ongoing trials	Phase	Reference
dsNKG2D-IL-15 fusion protein		Gastric		Enhanced NK cell tumour infiltration Supressed tumour growth				[167]
ALT-803	IL-15 super-agonist	Ovarian	Boosted cytotoxicity	Boosted cytotoxicity				[168].
ALT-803	IL-15 super-agonist	Breast		Supported NK cell expansion Boosted cytotoxicity		NCT03054909	1	[169]
ALT-803	IL-15 super-agonist	Colon		Supported NK cell expansion Boosted cytotoxicity				[169]
CIML NK Cells		Ovarian		Enhanced IFN-γ production and killing of target cells				
CIML NK Cells		Multiple Myeloma				NCT04634435	1/2	
NKTR-214	Pegylated IL-2	Breast and colorectal			Tumour shrinkage Stable disease Increased peripheral NK frequency			[175]
NKTR-214 + nivolumab	Pegylated IL-2 + PD-1 ICI	Breast and colorectal			Complete response 18.9%	NCT03435640 NCT02869295	1/2 1/2	[178]
eUCB	IL-21 expanded Umbilical cord blood derived NK cells	Colorectal	Boosted cytotoxicity Enhanced IFN-γ and TNF-α production	HT29 model → Enhanced tumour infiltration Reduced tumour burden LoVo model → Poor infiltration No tumour shrinkage				[179]
eUCB + bevacizumab	IL-21 expanded Umbilical cord blood derived NK cells + *anti*-VEGF	Colorectal		LoVo model → enhanced tumour infiltration Reduced tumour burden		NCT02857920	1/2	[179]
haNK + ALT-803 + avelumab + chemotherapy combination	$CD16^+$ NK-92 + IL-15 super-agonist + PD-1 ICI	Pancreatic			SD 75% Median PFS 7.1 months Median OS 8.2 months	NCT03586869	1/2	[180]
haNK + N-803 + avelumab + chemotherapy combination	$CD16^+$ NK-92 + IL-15 super-agonist + PD-1 ICI	Breast Cancer			CD 78% OR 67% Median PFS 13 months	NCT03387085	1/2	[181]
PD-L1-haNK + N-803	PD-L1- CAR $CD16^+$ NK-92 + IL-15 super-agonist	Pancreatic			80% of patients alive 8–16 months post treatment	NCT04390399	2	[182]
PD-L1 CAR-NK cells + pembrolizumab + N-803	PD-L1- CAR $CD16^+$ NK-92 + PD-1 ICI + IL-15 super-agonist	Gastric				NCT04847466	2	
NKG2D + IL-21 nanoparticle		Colon		Nanoparticle localised at tumour site Promoted NK cell tumour infiltration Stimulated NK cells				[183]

months (NCT03586869) (Table 4) [180]. In patients with relapsed metastatic triple negative breast cancer, haNK in combination with an IL-15 superagonist N-803, low dose chemoradiotherapy and a PD-L1 checkpoint inhibitor 78% of patients had controlled diseases and 67% had an overall response (NCT03387085) [181]. The median progression free survival exceeded 13 months compared to 2–3 months historically for pre-treated patients [181]. These results prompted the initiation of the QUILT 3.058, a phase 1b/2 trial examining chemotherapy, N-803 and PD-L1 t-haNK, with an antibody drug conjugate sacituzumab govitecan-hziy (NCT04927884) (Table 4). QUILT-88 examining PD-L1 t-haNK in combination with N-803 in pancreatic cancer is ongoing (NCT04390399). Early results are promising with 80% of pancreatic cancer patients being alive 8–16 months after beginning this treatment as a third line therapy. Interestingly, trials testing the efficacy of this combination as a first- and second-line treatment in pancreatic cancer are actively recruiting [182]. In gastric cancer, a PD-L1 CAR, pembrolizumab and N-803 are currently in trial (NCT04847466) (Table 4).

Nanoparticle-based therapies hold great promise for NK cell-based therapies. Nanoparticle-based delivery of NKG2D and IL-21 can both recognise tumour cells via NKG2D and activate NK cells and T cells via IL-21. In colon tumour bearing mice, these nanoparticles localised at the tumour site, promoting NK cell infiltration into the tumour and stimulated NK cell mediated responses [183].

5. Future avenues: using chemokine-targeted therapies to improve the efficacy of NK cell therapies

One major hurdle halting the success of immune cell therapy for solid tumours is their failure to reach and/or recognise the tumour, and their susceptibility to tumour-mediated immunosuppression. As such, biasing NK cell trafficking toward the tumour with therapeutic intent could aid in overcoming these hurdles. The ability of NK cells to home to and infiltrate tumour is dependent on chemokines secreted by the TME and receptors expressed by NK cells [184]. Alterations in the chemokine expression profile can facilitate immune escape via the recruitment of immunosuppressive cells and limiting the migration of anti-tumour immune cells [185]. Therefore, there is huge opportunity to therapeutically target these facets of the TME. Chemokines are acutely involved in many aspects of tumour biology, such as aiding in tumour neovascularisation, immune evasion, and cancer metastasis, thus chemokine-based therapies have the potential to be multi-faceted (Fig. 5) (Table 5).

5.1. Chemokine receptor antagonists

Plerixafor, a CXCR4 antagonist has been approved for mobilisation of haematopoietic stem cells for transplantation [184]. Interestingly, Plerixafor has been shown to mobilise CD56^{bright} NK cells in the peripheral blood [186] and is in clinical trials for patients with pancreatic, ovarian and colorectal cancer (NCT02179970). In colorectal and pancreatic cancer patients treated with Plerixafor, post-treatment biopsies had an integrated immune response as indicated by transcriptional analysis, compared to matched pre-treatment biopsies, suggesting CXCR4 signalling causes immune suppression by limiting the function of the tumour homing chemokine receptors [187]. Combination of the CXCR4 antagonist BL-8040 with pembrolizumab (*anti*-PD-1) in pancreatic cancer patients resulted in 31% of patients having stable diseases and 3.4% with partial response [188]. Importantly, it increases effector T cell infiltration and dampened MDSC infiltration into the tumour [188]. BL-8040 is undergoing clinical trial for patients with gastric, gastroesophageal or oesophageal cancer (NCT03281369). CXCR4 antagonist LY2510924, in combination with PD-L1 inhibitor durvalumab showed promising results in pancreatic cancer patients, with 44.4% of patients reporting stable disease [189]. CCR5 blockade with maraviroc, coupled with subsequent chemotherapy achieved partial response in previously refractory colorectal cancer in 60% of patients, and stable disease in 20% [190]. CXCR2 antagonist MK-7123 in combination with pembrolizumab in colorectal cancer is also undergoing clinical trial (NCT03473925). In metastatic breast cancer multi-drug chemokine modulation therapy is ongoing (NCT03599453).

Misdirected migration of NK cells and T cells to the omentum in the obesity-associated cancer oesophageal adenocarcinoma has been

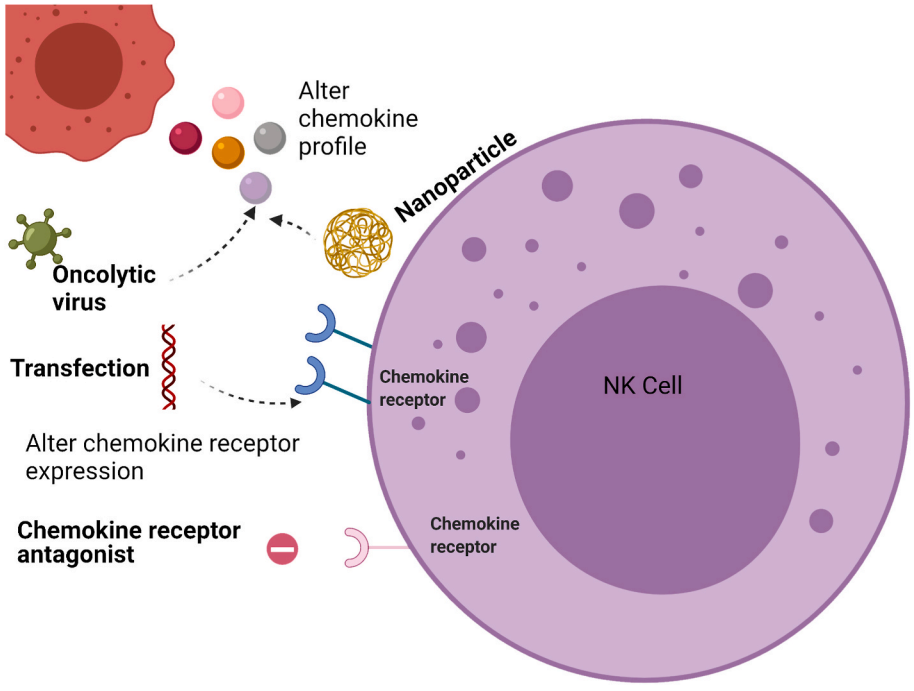

Fig. 5. ***Potential chemokine-based NK Cell immunotherapeutic approaches for obesity-associated cancer.*** Utilising chemokine receptor antagonists to promote migration of NK cells to the specific chemotactic cues of the tumour. Transfection of chemokine receptor mRNA into NK cells to express chemokine receptors. Alteration of the tumour chemokine signature using oncolytic viruses or nanoparticles. Created with BioRender.com.

Table 5
Chemokine based therapies *in vitro*, *in vivo* and in clinical trials. SD; Stable disease. PR; Partial response.

Agent	Target	Cancer	*In vitro*	*In vivo*	Trial	Ongoing trials	Phase	Reference
Chemokine Receptor antagonists								
Plerixafor	CXCR4 antagonist	Pancreatic Ovarian Colorectal				NCT02179970	1	
BL-8040	CXCR4 antagonist	Gastric, Gastroesophageal Oesophageal				NCT03281369	1/2	
BL-8040 + pembrolizumab	CXCR4 antagonist + PD-1 ICI	Pancreatic			31% SD 3.4% PR			[188]
MK-7123 + pembrolizumab	CXCR2 antagonist + PD-1 ICI	Colorectal				NCT03473925	2	
Multi-drug chemokine modulation		Breast				NCT03599453	1	
LY2510924 + durvalumab	CXCR4 antagonist + PD-1 ICI	Pancreatic			44.4% SD			[189]
Maraviroc	CCR5 antagonist	Colorectal			60% PR 20% SD			[190]
E6130	CX3CR1 antagonist	Oesophageal adenocarcinoma	Reduced NK cell migration to omentum					[12,100]
Genetically engineered chemokine receptor bearing NK cells								
CCR7$^+$ CAR-NK Cells	CCL19	CCL19$^+$ tumour	Enhanced ADCC Enhanced CCL19 migration					[193]
CCR7$^+$ NK cells	CCL19			144% increase in NK cell lymph node homing				[196]
CXCR3$^+$ NK cells	CXCL10	CXCL10$^+$ tumour		Enhanced infiltration Decreased tumour burden Prolonged survival				[197]
CXCR1$^+$ NKG2D CAR-NK cells		Ovarian		Enhanced infiltration Decreased tumour burden Prolonged survival				[198]
Oncolytic virus	CCL5	Colorectal	Enhanced CCR5$^+$ NK cell migration	Enhanced infiltration Decreased tumour growth				[200]

reported [77,191]. As such, the impact of the inflamed omentum in obesity-associated cancer cannot be ignored and should be targeted to increase efficacy of cell therapies. Antagonism of the chemokine receptor CX3CR1 has been shown to halt fractalkine-mediated NK cell migration towards the soluble chemotactic cues of the omentum, whilst maintaining migration towards the soluble chemotactic cues of the tumour [12]. Interestingly, exposure to the soluble microenvironment of the VAT hampers subsequent NK cell migration towards tumour, however this can be overcome by the use of a CX3CR1 antagonist [100]. This is further indication of the detrimental effects of the VAT on NK cell phenotype and function [12,77,100]. These studies suggests that CX3CR1 antagonism may offer a means to prevent the demise of NK cells in the omentum of obesity-associated cancer patients and redirect them towards the tumour to ultimately potentiate anti-tumour immunity.

5.2. Genetically engineered chemokine receptor bearing NK cells

While chemokine receptor antagonism shows extensive therapeutic potential in cancer, genetically engineering *ex vivo* expanded NK cells to express chemokine receptors is also being explored. Importantly, transfection of primary human NK cells with chemokine receptor mRNA has no deleterious effect on NK cell viability, phenotype and function [192–194]. NK cells transfected with chemokine receptors had improved migratory capacity *in vitro* toward their cognate ligands and was accompanied by altered adhesion properties and increased killing of target cells [192–194]. Treating NK cells with cationic nanoparticles increased cytotoxicity of NK cells towards breast cancer cells *in vivo*. This was accompanied by higher expression of CCR4 and CXCR4 on the surface of NK cells and resulted in improved trafficking of NK cells to the tumour [195]. Transfection with both CCR7 and CD16 improved NK cell migration toward CCL19 and enhanced ADCC *in vitro,* indicating that CAR-NK cells would be most efficacious with transfected chemokine receptors [193]. Induction of transient expression of CCR7 by trogocytosis resulted in enhanced migration of CCR7$^+$ NK cells toward CCL19 and CCL21, resulting in a 144% increase in NK cell lymph node homing in a mouse model. These data suggest rapid and transient modification of adoptive NK cells to enhance tumour homing, without the need for genetic alterations could be possible [196]. Adoptive transfer of *ex vivo* expanded CXCR3$^+$ NK cells resulted in enhanced NK cell infiltration into murine CXCL10$^+$ subcutaneous tumours. This was accompanied by a decreased tumour burden, and prolonged survival compared to their CXCL10$^-$ tumour bearing counterparts [197]. These data also highlight that eligibility for chemokine-receptor bearing NK cell therapies should consider chemokine tumour biomarkers to ensure appropriate patient stratification.

Combination therapies utilising CAR and chemokines have the potential to aid in trafficking and infiltration of NK cells into the solid tumour, a task which has otherwise proved difficult and one which could significantly enhance the effects of these immunotherapies. Primary NK cells transfected to express CXCR1 and *anti*-NKG2D CAR introduced into an ovarian cancer mouse model displayed superior tumour-infiltration, reduced tumour burden and prolonged survival compared to those treated with NKG2D-CAR-NK cells alone [198]. In a mouse model of glioma, the YTS NK cell line expressing both an *anti*-EGFR CAR and

CXCR4 exhibited significantly enhanced NK cell intratumoural frequency and improved overall survival [199].

5.3. Therapeutically altering the chemokine profile of the TME

In addition to chemokine receptor antagonists and transfection of NK cells with chemokine receptors, reinvigoration of *cold* tumours could be partly facilitated by altering their chemokine profile to recruit NK cells. Li et al. utilised an oncolytic virus to upregulate CCL5 in tumour cells, resulting in enhanced levels of $CCR5^+$ NK cell chemotaxis towards target cells *in vitro*. In a subcutaneous mouse model of colorectal cancer, oncolytic virus and adoptive NK cell transfer resulted in enhanced NK cell accumulation within the tumour and slowed tumour growth [200]. Other concepts to alter the chemokine expression of the tumour which are in early stages include epigenetic regulation of chemokine expression via epigenetic modulators and chemokine loaded hydrogels which promote the expansion and differentiation of T cells [201–203]. Immunomodulatory nanoparticles that can modify the tumour cell surface to express chemokine and activating receptors, can be employed to potentiate the anti-tumour response [202]. These nanoparticles could be co-opted to target a plethora of NK cell receptors and chemokines. Overall, these approaches could be used to manipulate the tumour microenvironment to attract the most cytotoxic immune populations into the solid tumour.

6. Challenges and considerations for NK cell therapies in and beyond obesity-associated cancers

NK cell therapies have several hurdles to overcome before they can be employed successfully as an immunotherapy with long lasting effects, both generally in solid tumours and in obesity associated cancers. As outlined in section 2.2 the solid tumour presents a series of challenges to NK cells which must be overcome through the generation of CAR-NK cell-based therapies and combination approaches. Immune escape mechanisms can be employed by the solid tumour to circumvent NK cell mediated effector responses and limit their trafficking. Therefore, the ICI- and chemokine-targeted approaches discussed above may prove invaluable in overcoming these hurdles. Approaches such as TGF-β type II targeting CAR-NK cells could overcome this immunosuppressive signalling and could become an indispensable element of CAR-NK cell generation [147].

Engraftment of the infused cell therapy is required for successful CAR-T cell treatment, however a durable engraftment of CAR-NK cells has yet to be reported. It is important to remember irradiated NK cell line-based therapies will not proliferate *in vivo* and overall the short lifespan of NK cells is a negative for durability of response. Innovative strategies to promote persistence and prolong efficacy must be delineated, including the use of cytokine superagonists and alternative sources and/or manipulations of NK cells. Cytokines are required to promote survival and thus *ex vivo* manipulation in the form of expansion of cell populations and activation of NK cells using cytokine cocktails or feeder cells is required [204,205]. Approaches such as CIML NK cells provide an opportunity to boost NK cell effector capacity and persistence by infusing CIML NK cells along with cytokine support in the form of IL-2.

Obesity-associated cancer presents a unique immunological landscape underpinned by the inter-relationship between obesity, the immune system and cancer. It is evident that this axis is both shaped by and further influences the profile of immune cells, including NK cells. This must be considered in the design of immunotherapies for the growing number of obesity-associated malignancies [206]. Therefore, it is paramount that the efficacy and safety of existing and novel immunotherapies and their effects on underlying inflammation are carefully scrutinised in obese cancer patients. Furthermore, the obese environment is altering NK cell phenotype and function as outlined in section 3 and therefore, NK cell responses may be compromised in obese patients with non-obesity associated cancers. Thus the approaches utilised for the treatment of obesity-associated cancers may be applied in this setting. Obesity status may need to be considered when selecting NK cell-based therapies for both obesity-associated cancer patients and obese patients with malignancies that are not considered obesity-associated. The obese metabolic microenvironment is believed to be mediating chronic immune dysfunction in obesity-associated cancer. This suggests that NK cells that are adoptively transferred into the obese cancer patient face a dysfunctional metabolic environment which may impact their phenotype, function and anti-tumour efficacy. Interestingly, a study by Lautenbach et al. showed that NK cells from normal-weight mice transferred into obese recipients did not exhibit obesity-induced dysfunction 72 h after infusion and instead maintained their previous "normal weight" phenotype, suggesting the obese environment may facilitate the adoptive transfer of NK cells, at least in the short term [207]. However further work into longer term effects of the obese environment on the phenotype of NK cells is needed, particularly in the setting of malignancy.

Checkpoint inhibition has been heralded as a breakthrough in cancer treatment but the potential for systemic PD-1 blockade to exacerbate existing systemic inflammation in an obese setting must be addressed. In OAC, our group reported that PD-1 blockade does not enhance T cell-mediated inflammation in the omentum, suggesting systemically administered PD-1/PD-L1 inhibition is unlikely to exacerbate pre-existing T cell-mediated inflammation outside of the tumour [208]. Indeed, in a large study of non-small cell lung cancer, melanoma and renal cell carcinoma patients, immune checkpoint inhibitors were more effective in patients with a BMI greater than 25 (overweight and obese), compared to their normal weight counterparts [209]. Therefore, obesity may be a positive prognostic factor for immunotherapeutic efficacy. Indeed, the obesity-associated alterations in NK cell phenotype and function make immune checkpoint inhibitors an attractive immunotherapeutic approach in obesity-associated cancer. Further research into the association between obesity and immune checkpoint inhibitor efficacy is warranted to delineate the relationship between these two factors.

Chemokine-targeted treatments are still predominantly in pre-clinical stages of development, however CXCR4, CCR5 and CXCR2 antagonists are in clinical trials. Targeting the chemokine system provides an excellent opportunity to boost NK cell migration to the solid tumour. This is an issue which has plagued cell-based therapies for solid tumours and hampered their success. Accurate profiling of the chemokine signature of different solid tumours and effector NK cells will be needed to target NK cell migration and bring chemokine-targeted treatments to the clinic. Our group has reported alterations in chemokine profiles across the disease sequence from healthy to Barrett's oesophagus and OAC, and differential expression across the different tissues of OAC patients [210]. For instance, the OAC tumour is enriched with CCL5, CCL3 and CCL20, making targeting these chemokines of interest [210]. Breast cancer tumours are known to be enriched with CCL2 whilst colorectal tumours are enriched with CCL20 [211,212]. The CXCL16 chemokine is abundant within pancreatic tumours [213]. Our group have identified the preferential migration of NK cells towards the soluble chemotactic cues of the omentum in OAC [77]. Once in the VAT, NK cell viability is compromised and a phenotypic shift occurs which may make NK cells less cytotoxic [12,77,100]. Furthermore, subsequent NK cell migration to the tumour is compromised following exposure to the VAT [100]. This places a key emphasis on preventing NK cell migration to the VAT. Our group have identified that the erroneous migration of NK cells to the omentum in OAC is governed by the CX3CR1:Fractalkine pathway and we have shown that antagonising this pathway can significantly reduce migration of NK cells towards the soluble cues of the omentum [12,100]. It is likely that a combination of chemokine receptor antagonists and CAR-NK cells will be required to ensure efficient trafficking of NK cells to the tumour and not the VAT or other compartments in obesity-associated cancer. Tumour antigen(s) and chemokine

receptor(s) CAR-NK cells could bridge this gap, and aid in the migration of NK cells to the tumour whilst boosting their effector function.

However, these combination therapies present their own challenges and the feasibility and cost-effectiveness of these therapies must be considered. Until durable patient responses have been achieved, NK cell-based therapies risk remaining as a niche market because the cost relative to the benefit may be prohibitive. However, the potential for NK cell-based therapies to become an *off-the-shelf* treatment is likely to reduce the cost of these therapies compared with their counterpart T cell-based therapies. Coupled with a greater awareness of immuno-therapies, this is likely to entice re-imbursement models to be agreed.

NK cells are crucial anti-tumour immune cells and augmenting their responses in cancer holds huge therapeutic value. However, they exhibit significantly impaired function in obesity and obesity-associated cancer. As such, further work is needed to delineate the extent of immune dysregulation in obesity-associated cancer and to phenotype the vast and unique subpopulations of NK cells to ensure that the most potent, anti-tumour NK cells are targeted for immunotherapeutic approaches. As obesity prevalence escalates, the rates of obesity-associated cancer are expected to increase in concert, thus making this a growing cancer cohort in need of new and innovative immunotherapeutic options.

Author contributions section

E. Mylod: Conceptualization, writing—original draft preparation, writing—review and editing. J. Lysaght: Conceptualization, writing—review and editing. M.J. Conroy: Conceptualization, writing—review and editing.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

E. Mylod is funded by Breakthrough Cancer Research (BCR-2019-02-PhD-TCD). All figures were created with biorender.com.

References

[1] B. Lauby-Secretan, C. Scoccianti, D. Loomis, Y. Grosse, F. Bianchini, K. Straif, Body fatness and cancer — viewpoint of the IARC working group, N. Engl. J. Med. 375 (2016) 794–798, https://doi.org/10.1056/NEJMsr1606602.

[2] K. Bhaskaran, I. Douglas, H. Forbes, I. Dos-Santos-Silva, D.A. Leon, L. Smeeth, Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults, Lancet 384 (2014) 755–765, https://doi.org/10.1016/S0140-6736(14)60892-8.

[3] A.G. Renehan, M. Tyson, M. Egger, R.F. Heller, M. Zwahlen, Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies, Lancet 371 (2008) 569–578, https://doi.org/10.1016/S0140-6736(08)60269-X.

[4] M.J. Markham, K. Wachter, N. Agarwal, M.M. Bertagnolli, S.M. Chang, W. Dale, C.S.M. Diefenbach, C. Rodriguez-Galindo, D.J. George, T.D. Gilligan, R. D. Harvey, M.L. Johnson, R.J. Kimple, M.A. Knoll, N. LoConte, R.G. Maki, J. L. Meisel, J.A. Meyerhardt, N.A. Pennell, G.B. Rocque, M.S. Sabel, R.L. Schilsky, B.J. Schneider, W.D. Tap, R.G. Uzzo, S.N. Westin, Clinical cancer advances 2020: annual report on progress against cancer from the American society of clinical oncology, J. Clin. Oncol. 38 (2020) 1081, https://doi.org/10.1200/JCO.19.03141.

[5] ASCO, Stomach Cancer: Statistics, Cancer.Net, 2021. www.cancer.net/cancer-types/stomach-cancer/statistics. (Accessed 14 October 2021).

[6] ASCO, Liver Cancer: Statistics, Cancer.Net, 2021. https://www.cancer.net/cancer-types/liver-cancer/statistics. (Accessed 14 October 2021).

[7] ASCO, Pancreatic Cancer: Statistics, Cancer.Net, 2021. https://www.cancer.net/cancer-types/pancreatic-cancer/statistics. (Accessed 14 October 2021).

[8] ASCO, Esophageal Cancer: Statistics, Cancer.Net (n.d.), https://www.cancer.net/cancer-types/esophageal-cancer/statistics. (Accessed 14 October 2021).

[9] J. Galon, D. Bruni, Approaches to treat immune hot, altered and cold tumours with combination immunotherapies, Nat. Rev. Drug Discov. 18 (2019) 197–218, https://doi.org/10.1038/s41573-018-0007-y.

[10] K. Muro, H.C. Chung, V. Shankaran, R. Geva, D. Catenacci, S. Gupta, J.P. Eder, T. Golan, D.T. Le, B. Burtness, A.J. McRee, C.-C. Lin, K. Pathiraja, J. Lunceford, K. Emancipator, J. Juco, M. Koshiji, Y.-J. Bang, Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial, Lancet Oncol. 17 (2016) 717–726, https://doi.org/10.1016/S1470-2045(16)00175-3.

[11] K. Shitara, M. Özgüroğlu, Y.-J. Bang, M. Di Bartolomeo, M. Mandalà, M.-H. Ryu, L. Fornaro, T. Olesiński, C. Caglevic, H.C. Chung, K. Muro, E. Goekkurt, W. Mansoor, R.S. McDermott, E. Shacham-Shmueli, X. Chen, C. Mayo, S.P. Kang, A. Ohtsu, C.S. Fuchs, G. Lerzo, J.M. O'Connor, G.A. Mendez, J. Lynam, N. Tebbutt, M. Wong, A. Strickland, C. Karapetis, D. Goldstein, P. Vasey, J.-L. Van Laethem, E. Van Cutsem, S. Berry, M. Vincent, B. Muller, F. Rey, A. Zambrano, J. Guerra, M. Krogh, L. Baeksgaard, M. Yilmaz, A. Elme, A. Magi, P. Auvinen, T. Alanko, M. Moehler, V. Kunzmann, T. Seufferlein, P. Thuss-Patience, E. Goekkurt, T. Hoehler, G. Haag, S.-E. Al-Batran, H. Castro, K. Lopez, M. Aguilar Vasquez, M. Sandoval, K.O. Lam, S. Cuffe, C. Kelly, R. Geva, E. Shacham-Shmueli, A. Hubert, A. Beny, B. Brenner, A. Giuseppe, A. Falcone, E. Maiello, R. Passalacqua, V. Montesarchio, H. Hara, K. Chin, T. Nishina, Y. Komatsu, N. Machida, S. Hironaka, T. Satoh, T. Tamura, N. Sugimoto, H. Cho, Y. Omuro, K. Kato, M. Goto, I. Hyodo, K. Yoshida, H. Baba, T. Esaki, J. Furuse, W.Z. Wan Mohammed, C. Hernandez Hernandez, J. Casas Garcia, A. Dominguez Andrade, K. Clarke, G. Hjortland, N. Glenjen, T. Kubiatowski, J. Jacek, M. Wojtukiewicz, S. Lazarev, Y. Lancukhay, S. Afanasayev, V. Moiseyenko, V. Kostorov, S. Protsenko, V. Shirinkin, D. Sakaeva, N. Fadeeva, W.P. Yong, C.H.M. Ng, B. Robertson, B. Rapaport, G. Cohen, L. Dreosti, P. Ruff, C. Jacobs, G. Landers, W. Szpak, S.-Y. Roh, J. Lee, Y.H. Kim, Y.-J. Bang, H.C. Chung, M.-H. Ryu, M. Alsina Maqueda, F. Longo Munoz, A. Cervantes Aguilar, E. Aranda Aguilar, P. Garcia Alfonso, F. Rivera, J. Feliu Batle, R. Pazo Cid, K.-H. Yeh, J.-S. Chen, Y. Chao, C.-J. Yen, M. Özgüroğlu, O. Kara, S. Yalcin, D. Hochhauser, I. Chau, A. Benson, V. Shankaran, W. Shaib, P. Philip, V. Sharma, R. Siegel, W. Sun, Z. Wainberg, B. George, A. Bullock, S. Myrick, J. Faruol, R. Siegel, T. Larson, C. Becerra, S. Ratnam, D.A. Richards, S.L. Riche, Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial, Lancet 392 (2018) 123–133, https://doi.org/10.1016/S0140-6736(18)31257-1.

[12] E. Mylod, A.M. Melo, N.E. Donlon, M. Davern, A. Bhardwaj, J.V. Reynolds, J. Lysaght, M.J. Conroy, Fractalkine elicits chemotactic, phenotypic, and functional effects on CX3CR1 + CD27 − NK cells in obesity-associated cancer, J. Immunol. 207 (2021) 1200–1210, https://doi.org/10.4049/jimmunol.2000987.

[13] C. Denkert, G. von Minckwitz, S. Darb-Esfahani, B. Lederer, B.I. Heppner, K. E. Weber, J. Budczies, J. Huober, F. Klauschen, J. Furlanetto, W.D. Schmitt, J.-U. Blohmer, T. Karn, B.M. Pfitzner, S. Kümmel, K. Engels, A. Schneeweiss, A. Hartmann, A. Noske, P.A. Fasching, C. Jackisch, M. van Mackelenbergh, P. Sinn, C. Schem, C. Hanusch, M. Untch, S. Loibl, Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy, Lancet Oncol. 19 (2018) 40–50, https://doi.org/10.1016/S1470-2045(17)30904-X.

[14] S.A. Pugh, R.J. Harrison, J.N. Primrose, S.I. Khakoo, T cells but not NK cells are associated with a favourable outcome for resected colorectal liver metastases, BMC Cancer 14 (2014) 180, https://doi.org/10.1186/1471-2407-14-180.

[15] N. Halama, M. Braun, C. Kahlert, A. Spille, C. Quack, N. Rahbari, M. Koch, J. Weitz, M. Kloor, I. Zoernig, P. Schirmacher, K. Brand, N. Grabe, C.S. Falk, Natural killer cells are scarce in colorectal carcinoma tissue despite high levels of chemokines and cytokines, Clin. Cancer Res. 17 (2011) 678–689, https://doi.org/10.1158/1078-0432.CCR-10-2173.

[16] S.K. Larsen, Y. Gao, P.H. Basse, NK cells in the tumor microenvironment, Crit. Rev. Oncog. 19 (2014) 91–105, https://doi.org/10.1615/CritRevOncog.2014011142.

[17] R.A. Soo, Z. Chen, R.S. Yan Teng, H.L. Tan, B. Iacopetta, B.C. Tai, R. Soong, Prognostic significance of immune cells in non-small cell lung cancer: meta-analysis, Oncotarget 9 (2018) 24801–24820, https://doi.org/10.18632/oncotarget.24835.

[18] J. Cursons, F. Souza-Fonseca-Guimaraes, M. Foroutan, A. Anderson, F. Hollande, S. Hediyeh-Zadeh, A. Behren, N.D. Huntington, M.J. Davis, A gene signature predicting natural killer cell infiltration and improved survival in melanoma patients, Cancer Immunol. Res. 7 (2019) 1162–1174, https://doi.org/10.1158/2326-6066.CIR-18-0500.

[19] J. Eckl, A. Buchner, P.U. Prinz, R. Riesenberg, S.I. Siegert, R. Kammerer, P. J. Nelson, E. Noessner, Transcript signature predicts tissue NK cell content and defines renal cell carcinoma subgroups independent of TNM staging, J. Mol. Med. 90 (2012) 55–66, https://doi.org/10.1007/s00109-011-0806-7.

[20] E. Vivier, E. Tomasello, M. Baratin, T. Walzer, S. Ugolini, Functions of natural killer cells, Nat. Immunol. 9 (2008) 503–510, https://doi.org/10.1038/ni1582.

[21] K. Imai, S. Matsuyama, S. Miyake, K. Suga, K. Nakachi, Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population, Lancet 356 (2000) 1795–1799, https://doi.org/10.1016/S0140-6736(00)03231-1.

[22] A. Silva, D.M. Andrews, A.G. Brooks, M.J. Smyth, Y. Hayakawa, Application of CD27 as a marker for distinguishing human NK cell subsets, Int. Immunol. 20 (2008) 625–630, https://doi.org/10.1093/intimm/dxn022.

[23] J.J. Campbell, S. Qin, D. Unutmaz, D. Soler, K.E. Murphy, M.R. Hodge, L. Wu, E. C. Butcher, Unique subpopulations of CD56 + NK and NK-T peripheral blood lymphocytes identified by chemokine receptor expression repertoire, J. Immunol. 166 (2001) 6477–6482, https://doi.org/10.4049/jimmunol.166.11.6477.

[24] E.O. Long, H. Sik Kim, D. Liu, M.E. Peterson, S. Rajagopalan, Controlling natural killer cell responses: integration of signals for activation and inhibition, Annu. Rev. Immunol. 31 (2013) 227–258, https://doi.org/10.1146/annurev-immunol-020711-075005.
[25] M.J. Smyth, E. Cretney, J.M. Kelly, J.A. Westwood, S.E.A. Street, H. Yagita, K. Takeda, S.L.H.V. Dommelen, M.A. Degli-Esposti, Y. Hayakawa, Activation of NK cell cytotoxicity, Mol. Immunol. 42 (2005) 501–510, https://doi.org/10.1016/j.molimm.2004.07.034.
[26] L. Chiossone, M. Vienne, Y.M. Kerdiles, E. Vivier, Natural killer cell immunotherapies against cancer: checkpoint inhibitors and more, Semin, Immunol. 31 (2017) 55–63, https://doi.org/10.1016/j.smim.2017.08.003.
[27] W. Wang, A.K. Erbe, J.A. Hank, Z.S. Morris, P.M. Sondel, NK cell-mediated antibody-dependent cellular cytotoxicity in cancer immunotherapy, Front. Immunol. 6 (2015), https://doi.org/10.3389/fimmu.2015.00368.
[28] M.A. Caligiuri, Human natural killer cells, Blood 112 (2008) 461–469, https://doi.org/10.1182/blood-2007-09-077438.
[29] J. Calmeiro, M. Carrascal, C. Gomes, A. Falcão, M.T. Cruz, B.M. Neves, Highlighting the role of DC-NK cell interplay in immunobiology and immunotherapy, in: Dendritic Cells, InTech, 2018, https://doi.org/10.5772/intechopen.78804.
[30] J.P. Böttcher, E. Bonavita, P. Chakravarty, H. Blees, M. Cabeza-Cabrerizo, S. Sammicheli, N.C. Rogers, E. Sahai, S. Zelenay, C. Reis e Sousa, NK cells stimulate recruitment of cDC1 into the tumor microenvironment promoting cancer immune control, Cell 172 (2018) 1022–1037, https://doi.org/10.1016/j.cell.2018.01.004, e14.
[31] K.C. Barry, J. Hsu, M.L. Broz, F.J. Cueto, M. Binnewies, A.J. Combes, A.E. Nelson, K. Loo, R. Kumar, M.D. Rosenblum, M.D. Alvarado, D.M. Wolf, D. Bogunovic, N. Bhardwaj, A.I. Daud, P.K. Ha, W.R. Ryan, J.L. Pollack, B. Samad, S. Asthana, V. Chan, M.F. Krummel, A natural killer–dendritic cell axis defines checkpoint therapy–responsive tumor microenvironments, Nat. Med. 24 (2018) 1178–1191, https://doi.org/10.1038/s41591-018-0085-8.
[32] J.L. Wong, E. Berk, R.P. Edwards, P. Kalinski, IL-18–Primed helper NK cells collaborate with dendritic cells to promote recruitment of effector CD8 + T cells to the tumor microenvironment, Cancer Res. 73 (2013) 4653–4662, https://doi.org/10.1158/0008-5472.CAN-12-4366.
[33] F. Gerosa, B. Baldani-Guerra, C. Nisii, V. Marchesini, G. Carra, G. Trinchieri, Reciprocal activating interaction between natural killer cells and dendritic cells, J. Exp. Med. 195 (2002) 327–333, https://doi.org/10.1084/jem.20010938.
[34] G. Ferlazzo, M. Pack, D. Thomas, C. Paludan, D. Schmid, T. Strowig, G. Bougras, W.A. Muller, L. Moretta, C. Munz, Distinct roles of IL-12 and IL-15 in human natural killer cell activation by dendritic cells from secondary lymphoid organs, Proc. Natl. Acad. Sci. Unit. States Am. 101 (2004) 16606–16611, https://doi.org/10.1073/pnas.0407522101.
[35] G. Ferlazzo, B. Morandi, Cross-talks between natural killer cells and distinct subsets of dendritic cells, Front. Immunol. 5 (2014), https://doi.org/10.3389/fimmu.2014.00159.
[36] T. Dao, M. Gomez-Nunez, C. Antczak, B. Kappel, J.S. Jaggi, T. Korontsvit, V. Zakhaleva, D.A. Scheinberg, Natural killer cells license dendritic cell cross-presentation of B lymphoma cell–associated antigens, Clin. Cancer Res. 11 (2005) 8763–8772, https://doi.org/10.1158/1078-0432.CCR-05-0975.
[37] O. Melaiu, V. Lucarini, L. Cifaldi, D. Fruci, Influence of the tumor microenvironment on NK cell function in solid tumors, Front. Immunol. 10 (2020) 3038, https://doi.org/10.3389/fimmu.2019.03038.
[38] I. Waldhauer, D. Goehlsdorf, F. Gieseke, T. Weinschenk, M. Wittenbrink, A. Ludwig, S. Stevanovic, H.G. Rammensee, A. Steinle, Tumor-associated MICA is shed by ADAM proteases, Cancer Res. 68 (2008) 6368–6376, https://doi.org/10.1158/0008-5472.CAN-07-6768.
[39] E. Schlecker, N. Fiegler, A. Arnold, P. Altevogt, S. Rose-John, G. Moldenhauer, A. Sucker, A. Paschen, E.P. von Strandmann, S. Textor, A. Cerwenka, Metalloprotease-mediated tumor cell shedding of B7-H6, the ligand of the natural killer cell–activating receptor NKp30, Cancer Res. 74 (2014) 3429–3440, https://doi.org/10.1158/0008-5472.CAN-13-3017.
[40] M. Balsamo, W. Vermi, M. Parodi, G. Pietra, C. Manzini, P. Queirolo, S. Lonardi, R. Augugliaro, A. Moretta, F. Facchetti, L. Moretta, M.C. Mingari, M. Vitale, Melanoma cells become resistant to NK-cell-mediated killing when exposed to NK-cell numbers compatible with NK-cell infiltration in the tumor, Eur. J. Immunol. 42 (2012) 1833–1842, https://doi.org/10.1002/eji.201142179.
[41] L. Zitvogel, A. Tesniere, G. Kroemer, Cancer despite immunosurveillance: immunoselection and immunosubversion, Nat. Rev. Immunol. 6 (2006) 715–727, https://doi.org/10.1038/nri1936.
[42] J.A. Gubbels, M. Felder, S. Horibata, J.A. Belisle, A. Kapur, H. Holden, S. Petrie, M. Migneault, C. Rancourt, J.P. Connor, M.S. Patankar, MUC16 provides immune protection by inhibiting synapse formation between NK and ovarian tumor cells, Mol. Cancer 9 (2010) 11, https://doi.org/10.1186/1476-4598-9-11.
[43] R. Castriconi, C. Cantoni, M. Della Chiesa, M. Vitale, E. Marcenaro, R. Conte, R. Biassoni, C. Bottino, L. Moretta, A. Moretta, Transforming growth factor β1 inhibits expression of NKP30 and NKG2D receptors: consequences for the NK-mediated killing of dendritic cells, Proc. Natl. Acad. Sci. U.S.A. 100 (2003) 4120–4125, https://doi.org/10.1073/pnas.0730640100.
[44] C.A. Crane, S.J. Han, J.J. Barry, B.J. Ahn, L.L. Lanier, A.T. Parsa, TGF-downregulates the activating receptor NKG2D on NK cells and CD8+ T cells in glioma patients, Neuro Oncol. 12 (2010) 7–13, https://doi.org/10.1093/neuonc/nop009.
[45] Y. Gao, F. Souza-Fonseca-Guimaraes, T. Bald, S.S. Ng, A. Young, S.F. Ngiow, J. Rautela, J. Straube, N. Waddell, S.J. Blake, J. Yan, L. Bartholin, J.S. Lee, E. Vivier, K. Takeda, M. Messaoudene, L. Zitvogel, M.W.L. Teng, G.T. Belz, C. R. Engwerda, N.D. Huntington, K. Nakamura, M. Hölzel, M.J. Smyth, Tumor immunoevasion by the conversion of effector NK cells into type 1 innate lymphoid cells, Nat, Immunol. 18 (2017) 1004–1015, https://doi.org/10.1038/ni.3800.
[46] R. Trotta, J.D. Col, J. Yu, D. Ciarlariello, B. Thomas, X. Zhang, J. Allard, M. Wei, H. Mao, J.C. Byrd, D. Perrotti, M.A. Caligiuri, TGF-β utilizes SMAD3 to inhibit CD16-mediated IFN-γ production and antibody-dependent cellular cytotoxicity in human NK cells, J. Immunol. 181 (2008) 3784–3792, https://doi.org/10.4049/jimmunol.181.6.3784.
[47] A.H. Rook, J.H. Kehrl, L.M. Wakefield, A.B. Roberts, M.B. Sporn, D.B. Burlington, H.C. Lane, A.S. Fauci, Effects of transforming growth factor beta on the functions of natural killer cells: depressed cytolytic activity and blunting of interferon responsiveness, J. Immunol. 136 (1986) 3916 LP–3920. http://www.jimmunol.org/content/136/10/3916.abstract.
[48] S. Viel, A. Marçais, F.S.-F. Guimaraes, R. Loftus, J. Rabilloud, M. Grau, S. Degouve, S. Djebali, A. Sanlaville, E. Charrier, J. Bienvenu, J.C. Marie, C. Caux, J. Marvel, L. Town, N.D. Huntington, L. Bartholin, D. Finlay, M.J. Smyth, T. Walzer, TGF-β inhibits the activation and functions of NK cells by repressing the mTOR pathway, Sci. Signal. 9 (2016), https://doi.org/10.1126/scisignal.aad1884.
[49] J. Cong, X. Wang, X. Zheng, D. Wang, B. Fu, R. Sun, Z. Tian, H. Wei, Dysfunction of natural killer cells by FBP1-induced inhibition of glycolysis during lung cancer progression, Cell Metabol. 28 (2018) 243–255, https://doi.org/10.1016/j.cmet.2018.06.021, e5.
[50] K. Slattery, E. Woods, V. Zaiatz-Bittencourt, S. Marks, S. Chew, M. Conroy, C. Goggin, C. MacEochagain, J. Kennedy, S. Lucas, D.K. Finlay, C.M. Gardiner, TGFβ drives NK cell metabolic dysfunction in human metastatic breast cancer, J. Immunother. Cancer. 9 (2021), https://doi.org/10.1136/jitc-2020-002044.
[51] S.E. Keating, V. Zaiatz-Bittencourt, R.M. Loftus, C. Keane, K. Brennan, D. K. Finlay, C.M. Gardiner, Metabolic reprogramming supports IFN-γ production by CD56 bright NK cells, J. Immunol. 196 (2016) 2552–2560, https://doi.org/10.4049/jimmunol.1501783.
[52] R.P. Donnelly, R.M. Loftus, S.E. Keating, K.T. Liou, C.A. Biron, C.M. Gardiner, D. K. Finlay, mTORC1-Dependent metabolic reprogramming is a prerequisite for NK cell effector function, J. Immunol. 193 (2014) 4477–4484, https://doi.org/10.4049/jimmunol.1401558.
[53] C.-H. Chang, J. Qiu, D. O'Sullivan, M.D. Buck, T. Noguchi, J.D. Curtis, Q. Chen, M. Gindin, M.M. Gubin, G.J.W. van der Windt, E. Tonc, R.D. Schreiber, E. J. Pearce, E.L. Pearce, Metabolic competition in the tumor microenvironment is a driver of cancer progression, Cell 162 (2015) 1229–1241, https://doi.org/10.1016/j.cell.2015.08.016.
[54] X. Michelet, L. Dyck, A. Hogan, R.M. Loftus, D. Duquette, K. Wei, S. Beyaz, A. Tavakkoli, C. Foley, R. Donnelly, C. O'Farrelly, M. Raverdeau, A. Vernon, W. Pettee, D. O'Shea, B.S. Nikolajczyk, K.H.G. Mills, M.B. Brenner, D. Finlay, L. Lynch, Metabolic reprogramming of natural killer cells in obesity limits antitumor responses, Nat. Immunol. 19 (2018) 1330–1340, https://doi.org/10.1038/s41590-018-0251-7.
[55] C. Harmon, M.W. Robinson, F. Hand, D. Almuaili, K. Mentor, D.D. Houlihan, E. Hoti, L. Lynch, J. Geoghegan, C. O'Farrelly, Lactate-mediated acidification of tumor microenvironment induces apoptosis of liver-resident NK cells in colorectal liver metastasis, Cancer Immunol. Res. 7 (2019) 335–346, https://doi.org/10.1158/2326-6066.CIR-18-0481.
[56] Z. Husain, Y. Huang, P. Seth, V.P. Sukhatme, Tumor-derived lactate modifies antitumor immune response: effect on myeloid-derived suppressor cells and NK cells, J. Immunol. 191 (2013) 1486–1495, https://doi.org/10.4049/jimmunol.1202702.
[57] A.E. Vilgelm, A. Richmond, Chemokines modulate immune surveillance in tumorigenesis, metastasis, and response to immunotherapy, Front. Immunol. 10 (2019), https://doi.org/10.3389/fimmu.2019.00333.
[58] A. Bikfalvi, C. Billottet, The CC and CXC chemokines: major regulators of tumor progression and the tumor microenvironment, Am. J. Physiol. Physiol. 318 (2020) C542–C554, https://doi.org/10.1152/ajpcell.00378.2019.
[59] B. Bierie, C.H. Chung, J.S. Parker, D.G. Stover, N. Cheng, A. Chytil, M. Aakre, Y. Shyr, H.L. Moses, Abrogation of TGF-β signaling enhances chemokine production and correlates with prognosis in human breast cancer, J. Clin. Invest. 119 (2009) 1571–1582, https://doi.org/10.1172/JCI37480.
[60] M. Taki, K. Abiko, T. Baba, J. Hamanishi, K. Yamaguchi, R. Murakami, K. Yamanoi, N. Horikawa, Y. Hosoe, E. Nakamura, A. Sugiyama, M. Mandai, I. Konishi, N. Matsumura, Snail promotes ovarian cancer progression by recruiting myeloid-derived suppressor cells via CXCR2 ligand upregulation, Nat. Commun. 9 (2018), https://doi.org/10.1038/s41467-018-03966-7.
[61] H. Katoh, D. Wang, T. Daikoku, H. Sun, S.K. Dey, R.N. DuBois, CXCR2-Expressing myeloid-derived suppressor cells are essential to promote colitis-associated tumorigenesis, Cancer Cell 24 (2013) 631–644, https://doi.org/10.1016/j.ccr.2013.10.009.
[62] B. Huang, Z. Lei, J. Zhao, W. Gong, J. Liu, Z. Chen, Y. Liu, D. Li, Y. Yuan, G. M. Zhang, Z.H. Feng, CCL2/CCR2 pathway mediates recruitment of myeloid suppressor cells to cancers, Cancer Lett. 252 (2007) 86–92, https://doi.org/10.1016/j.canlet.2006.12.012.
[63] M. Balsamo, C. Manzini, G. Pietra, F. Raggi, F. Blengio, M.C. Mingari, L. Varesio, L. Moretta, M.C. Bosco, M. Vitale, Hypoxia downregulates the expression of activating receptors involved in NK-cell-mediated target cell killing without affecting ADCC, Eur. J. Immunol. 43 (2013) 2756–2764, https://doi.org/10.1002/eji.201343448.
[64] P. Sinha, V.K. Clements, S.K. Bunt, S.M. Albelda, S. Ostrand-Rosenberg, Cross-talk between myeloid-derived suppressor cells and macrophages subverts tumor

immunity toward a type 2 response, J. Immunol. 179 (2007) 977–983, https://doi.org/10.4049/jimmunol.179.2.977.
[65] H. Li, Y. Han, Q. Guo, M. Zhang, X. Cao, Cancer-expanded myeloid-derived suppressor cells induce anergy of NK cells through membrane-bound TGF-β1, J. Immunol. 182 (2009) 240–249, https://doi.org/10.4049/jimmunol.182.1.240.
[66] L. Ren, Y. Yu, L. Wang, Z. Zhu, R. Lu, Z. Yao, Hypoxia-induced CCL28 promotes recruitment of regulatory T cells and tumor growth in liver cancer, Oncotarget 7 (2016) 75763–75773, https://doi.org/10.18632/oncotarget.12409.
[67] H. Kinoshita, M. Yashiro, T. Fukuoka, T. Hasegawa, T. Morisaki, H. Kasashima, G. Masuda, S. Noda, K. Hirakawa, Diffuse-type gastric cancer cells switch their driver pathways from FGFR2 signaling to SDF1/CXCR4 axis in hypoxic tumor microenvironments, Carcinogenesis (2015), bgv134, https://doi.org/10.1093/carcin/bgv134.
[68] B. Müller, B. Fischer, W. Kreutz, An acidic microenvironment impairs the generation of non-major histocompatibility complex-restricted killer cells, Immunology 99 (2000) 375–384, https://doi.org/10.1046/j.1365-2567.2000.00975.x.
[69] A.J. Thistlethwaite, D.B. Leeper, D.J. Moylan, R.E. Nerlinger, pH distribution in human tumors, Int. J. Radiat. Oncol. 11 (1985) 1647–1652, https://doi.org/10.1016/0360-3016(85)90217-2.
[70] I. Terrén, A. Orrantia, J. Vitallé, O. Zenarruzabeitia, F. Borrego, NK cell metabolism and tumor microenvironment, Front. Immunol. 10 (2019), https://doi.org/10.3389/fimmu.2019.02278.
[71] C.L. Donohoe, J. Lysaght, J. O'Sullivan, J.V. Reynolds, Emerging concepts linking obesity with the hallmarks of cancer, Trends Endocrinol. Metabol. (2017), https://doi.org/10.1016/j.tem.2016.08.004.
[72] T. Deng, C.J. Lyon, S. Bergin, M.A. Caligiuri, W.A. Hsueh, Obesity, inflammation, and cancer, Annu. Rev. Pathol. 11 (2016) 421–449, https://doi.org/10.1146/annurev-pathol-012615-044359.
[73] F.M. Wensveen, S. Valentić, M. Šestan, T. Turk Wensveen, B. Polić, The "Big Bang" in obese fat: events initiating obesity-induced adipose tissue inflammation, Eur. J. Immunol. 45 (2015) 2446–2456, https://doi.org/10.1002/eji.201545502.
[74] A.M. Melo, E. Mylod, V. Fitzgerald, N.E. Donlon, D.M. Murphy, E.K. Foley, A. Bhardwaj, J.V. Reynolds, D.G. Doherty, J. Lysaght, M.R. Dunne, M.J. Conroy, Tissue distribution of γδ T cell subsets in oesophageal adenocarcinoma, Clin. Immunol. 229 (2021), 108797, https://doi.org/10.1016/j.clim.2021.108797.
[75] M.J. Conroy, S.G. Maher, A.M. Melo, S.L. Doyle, E. Foley, J.V. Reynolds, A. Long, J. Lysaght, Identifying a novel role for fractalkine (CX3CL1) in memory CD8+ T cell accumulation in the omentum of obesity-associated cancer patients, Front. Immunol. 9 (2018), https://doi.org/10.3389/fimmu.2018.01867.
[76] A.M. Melo, A.M. O'Brien, J.J. Phelan, S.A. Kennedy, N.A.W. Wood, N. Veerapen, G.S. Besra, N.E. Clarke, E.K. Foley, A. Ravi, F. MacCarthy, D. O'Toole, N. Ravi, J. V. Reynolds, M.J. Conroy, A.E. Hogan, J. O'Sullivan, M.R. Dunne, Mucosal-associated invariant T cells display diminished effector capacity in oesophageal adenocarcinoma, Front. Immunol. 10 (2019), https://doi.org/10.3389/fimmu.2019.01580.
[77] M.J. Conroy, V. Fitzgerald, S.L. Doyle, S. Channon, Z. Useckaite, N. Gilmartin, C. O'Farrelly, N. Ravi, J.V. Reynolds, J. Lysaght, The microenvironment of visceral adipose tissue and liver alter natural killer cell viability and function, J. Leukoc. Biol. 100 (2016) 1435–1442, https://doi.org/10.1189/jlb.5AB1115-493RR.
[78] M.J. Conroy, J. Lysaght, CX3CL1 signaling in the tumor microenvironment, in: Adv. Exp. Med. Biol, Springer, 2020, pp. 1–12, https://doi.org/10.1007/978-3-030-36667-4_1.
[79] D. O'Shea, A.E. Hogan, Dysregulation of natural killer cells in obesity, Cancers 11 (2019) 573, https://doi.org/10.3390/cancers11040573.
[80] I. Bähr, J. Spielmann, D. Quandt, H. Kielstein, Obesity-associated alterations of natural killer cells and immunosurveillance of cancer, Front. Immunol. 11 (2020), https://doi.org/10.3389/fimmu.2020.00245.
[81] L.A. Lynch, J.M. O'Connell, A.K. Kwasnik, T.J. Cawood, C. O'Farrelly, D. B. O'Shea, Are natural killer cells protecting the metabolically healthy obese patient? Obesity 17 (2009) 601–605, https://doi.org/10.1038/oby.2008.565.
[82] M. Kim, M. Kim, H.J. Yoo, J.H. Lee, Natural killer cell activity and interleukin-12 in metabolically healthy versus metabolically unhealthy overweight individuals, Front. Immunol. 8 (2017) 1700, https://doi.org/10.3389/fimmu.2017.01700.
[83] L.M. Tobin, M. Mavinkurve, E. Carolan, D. Kinlen, E.C. O'Brien, M.A. Little, D. K. Finlay, D. Cody, A.E. Hogan, D. O'Shea, NK cells in childhood obesity are activated, metabolically stressed, and functionally deficient, JCI Insight 2 (2017), https://doi.org/10.1172/jci.insight.94939.
[84] S. Viel, L. Besson, E. Charrier, A. Marçais, E. Disse, J. Bienvenu, T. Walzer, C. Dumontet, Alteration of Natural Killer cell phenotype and function in obese individuals, Clin. Immunol. 177 (2017) 12–17, https://doi.org/10.1016/j.clim.2016.01.007.
[85] I. Bähr, J. Jahn, A. Zipprich, I. Pahlow, J. Spielmann, H. Kielstein, Impaired natural killer cell subset phenotypes in human obesity, Immunol. Res. 66 (2018) 234–244, https://doi.org/10.1007/s12026-018-8989-4.
[86] W. Naujoks, D. Quandt, A. Hauffe, H. Kielstein, I. Bähr, J. Spielmann, Characterization of surface receptor expression and cytotoxicity of human NK cells and NK cell subsets in overweight and obese humans, Front. Immunol. 11 (2020), https://doi.org/10.3389/fimmu.2020.573200.
[87] T. Laue, C.D. Wrann, B. Hoffmann-Castendiek, D. Pietsch, L. Hübner, H. Kielstein, Altered NK cell function in obese healthy humans, BMC Obes 2 (2015) 1, https://doi.org/10.1186/s40608-014-0033-1.
[88] D. O'Shea, T.J. Cawood, C. O'Farrelly, L. Lynch, Natural killer cells in obesity: impaired function and increased susceptibility to the effects of cigarette smoke, PLoS One 5 (2010), e8660, https://doi.org/10.1371/journal.pone.0008660.
[89] R.W. O'Rourke, G.D. Gaston, K.A. Meyer, A.E. White, D.L. Marks, Adipose tissue NK cells manifest an activated phenotype in human obesity, Metabolism 62 (2013) 1557–1561, https://doi.org/10.1016/j.metabol.2013.07.011.
[90] A.D. Hildreth, F. Ma, Y.Y. Wong, R. Sun, M. Pellegrini, T.E. O'Sullivan, Single-cell sequencing of human white adipose tissue identifies new cell states in health and obesity, Nat. Immunol. 22 (2021) 639–653, https://doi.org/10.1038/s41590-021-00922-4.
[91] A.O. Cuff, F. Sillito, S. Dertschnig, A. Hall, T.V. Luong, R. Chakraverty, V. Male, The obese liver environment mediates conversion of NK cells to a less cytotoxic ILC1-like phenotype, Front. Immunol. 10 (2019), https://doi.org/10.3389/fimmu.2019.02180.
[92] F.M. Wensveen, V. Jelenčić, S. Valentić, M. Šestan, T.T. Wensveen, S. Theurich, A. Glasner, D. Mendrila, D. Štimac, F.T. Wunderlich, J.C. Brüning, O. Mandelboim, B. Polić, NK cells link obesity-induced adipose stress to inflammation and insulin resistance, Nat. Immunol. 16 (2015) 376–385, https://doi.org/10.1038/ni.3120.
[93] B.C. Lee, M.S. Kim, M. Pae, Y. Yamamoto, D. Eberlé, T. Shimada, N. Kamei, H. S. Park, S. Sasorith, J.R. Woo, J. You, W. Mosher, H.J.M. Brady, S.E. Shoelson, J. Lee, Adipose natural killer cells regulate adipose tissue macrophages to promote insulin resistance in obesity, Cell Metabol. 23 (2016) 685–698, https://doi.org/10.1016/j.cmet.2016.03.002.
[94] S. Theurich, E. Tsaousidou, R. Hanssen, A.M. Lempradl, J. Mauer, K. Timper, K. Schilbach, K. Folz-Donahue, C. Heilinger, V. Sexl, J.A. Pospisilik, F. T. Wunderlich, J.C. Brüning, IL-6/Stat3-Dependent induction of a distinct, obesity-associated NK cell subpopulation deteriorates energy and glucose homeostasis, Cell Metabol. 26 (2017) 171–184, https://doi.org/10.1016/j.cmet.2017.05.018, e6.
[95] R.W. O'Rourke, K.A. Meyer, C.K. Neeley, G.D. Gaston, P. Sekhri, M. Szumowski, B. Zamarron, C.N. Lumeng, D.L. Marks, Systemic NK cell ablation attenuates intra-abdominal adipose tissue macrophage infiltration in murine obesity, Obesity 22 (2014) 2109–2114, https://doi.org/10.1002/oby.20823.
[96] T.E. O'Sullivan, M. Rapp, X. Fan, O.-E. Weizman, P. Bhardwaj, N.M. Adams, T. Walzer, A.J. Dannenberg, J.C. Sun, Adipose-resident group 1 innate lymphoid cells promote obesity-associated insulin resistance, Immunity 45 (2016) 428–441, https://doi.org/10.1016/j.immuni.2016.06.016.
[97] K. Wouters, Y.H.A.M. Kusters, M. Bijnen, S. Wetzels, X. Zhang, P.B.C. Linssen, K. Gaens, A.J.H.M. Houben, P.J. Joris, J. Plat, M.E. Kooi, C.J.H. Kallen, R. P. Mensink, K. Verboven, J. Jocken, D. Hansen, E.E. Blaak, F.A.I. Ehlers, L. Wieten, J.W. Greve, S. Rensen, C.D.A. Stehouwer, C.G. Schalkwijk, NK cells in human visceral adipose tissue contribute to obesity-associated insulin resistance through low-grade inflammation, Clin. Transl. Med. 10 (2020), https://doi.org/10.1002/ctm2.192.
[98] B.S. Hamilton, D. Paglia, A.Y.M. Kwan, M. Deitel, Increased obese mRNA expression in omental fat cells from massively obese humans, Nat. Med. 1 (1995) 953–956, https://doi.org/10.1038/nm0995-953.
[99] C.D. Wrann, T. Laue, L. Hübner, S. Kuhlmann, R. Jacobs, L. Goudeva, H. Nave, Short-term and long-term leptin exposure differentially affect human natural killer cell immune functions, Am. J. Physiol. Endocrinol. Metab. 302 (2012), https://doi.org/10.1152/ajpendo.00057.2011.
[100] E. Mylod, F. O'Connell, N.E. Donlon, C. Butler, J.V. Reynolds, J. Lysaght, M. J. Conroy, The omentum in obesity-associated cancer: a hindrance to effective natural killer cell migration towards tumour which can Be overcome by CX3CR1 antagonism, Cancers 14 (2021) 64, https://doi.org/10.3390/cancers14010064.
[101] I. Bähr, O.J. Pörtner, M. Glass, H. Doberstein, V. Goritz, G.G.R. Hiller, J. Spielmann, H. Kielstein, Characterization of natural killer cells in colorectal tumor tissue of rats fed a control diet or a high-fat diet, Ann. Anat. - Anat. Anzeiger. 233 (2021), 151586, https://doi.org/10.1016/j.aanat.2020.151586.
[102] N. Halama, M. Braun, C. Kahlert, A. Spille, C. Quack, N. Rahbari, M. Koch, J. Weitz, M. Kloor, I. Zoernig, P. Schirmacher, K. Brand, N. Grabe, C.S. Falk, Natural killer cells are scarce in colorectal carcinoma tissue despite high levels of chemokines and cytokines, Clin. Cancer Res. 17 (2011) 678–689, https://doi.org/10.1158/1078-0432.CCR-10-2173.
[103] I. Bähr, V. Goritz, H. Doberstein, G.G.R. Hiller, P. Rosenstock, J. Jahn, O. Pörtner, T. Berreis, T. Mueller, J. Spielmann, H. Kielstein, Diet-induced obesity is associated with an impaired NK cell function and an increased colon cancer incidence, J. Nutr. Metab. (2017), 4297025, https://doi.org/10.1155/2017/4297025, 2017.
[104] C. Degos, M. Heinemann, J. Barrou, N. Boucherit, E. Lambaudie, A. Savina, L. Gorvel, D. Olive, Endometrial tumor microenvironment alters human NK cell recruitment, and resident NK cell phenotype and function, Front. Immunol. 10 (2019), https://doi.org/10.3389/fimmu.2019.00877.
[105] N. Stanietsky, H. Simic, J. Arapovic, A. Toporik, O. Levy, A. Novik, Z. Levine, M. Beiman, L. Dassa, H. Achdout, N. Stern-Ginossar, P. Tsukerman, S. Jonjic, O. Mandelboim, The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity, Proc. Natl. Acad. Sci. U.S.A. 106 (2009) 17858–17863, https://doi.org/10.1073/pnas.0903474106.
[106] M. Li, P. Xia, Y. Du, S. Liu, G. Huang, J. Chen, H. Zhang, N. Hou, X. Cheng, L. Zhou, P. Li, X. Yang, Z. Fan, T-cell immunoglobulin and ITIM domain (TIGIT) receptor/poliovirus receptor (PVR) ligand engagement suppresses interferon-γ production of natural killer cells via β-arrestin 2-mediated negative signaling, J. Biol. Chem. 289 (2014) 17647–17657, https://doi.org/10.1074/jbc.M114.572420.
[107] Q. Zhang, J. Bi, X. Zheng, Y. Chen, H. Wang, W. Wu, Z. Wang, Q. Wu, H. Peng, H. Wei, R. Sun, Z. Tian, Blockade of the checkpoint receptor TIGIT prevents NK cell exhaustion and elicits potent anti-tumor immunity, Nat. Immunol. 19 (2018) 723–732, https://doi.org/10.1038/s41590-018-0132-0.

[108] L. Dyck, H. Prendeville, M. Raverdeau, M.M. Wilk, R.M. Loftus, A. Douglas, J. McCormack, B. Moran, M. Wilkinson, E.L. Mills, M. Doughty, A. Fabre, H. Heneghan, C. LeRoux, A. Hogan, E.T. Chouchani, D. O'Shea, D. Brennan, L. Lynch, Suppressive effects of the obese tumor microenvironment on CD8 T cell infiltration and effector function, J. Exp. Med. 219 (2022), e20210042, https://doi.org/10.1084/jem.20210042.

[109] J. Spielmann, L. Mattheis, J.-S. Jung, H. Rauße, M. Glaß, I. Bähr, D. Quandt, J. Oswald, H. Kielstein, Effects of obesity on NK cells in a mouse model of postmenopausal breast cancer, Sci. Rep. 10 (2020), 20606, https://doi.org/10.1038/s41598-020-76906-5.

[110] J. Spielmann, J. Hanke, D. Knauf, S. Ben-Eliyahu, R. Jacobs, G.I. Stangl, I. Bähr, H. Kielstein, Significantly enhanced lung metastasis and reduced organ NK cell functions in dietinduced obese rats, BMC Obes 4 (2017) 24, https://doi.org/10.1186/s40608-017-0161-5.

[111] E.J. Kim, M.-R. Choi, H. Park, M. Kim, J.E. Hong, J.-Y. Lee, H.S. Chun, K.W. Lee, J. H. Yoon Park, Dietary fat increases solid tumor growth and metastasis of 4T1 murine mammary carcinoma cells and mortality in obesity-resistant BALB/c mice, Breast Cancer Res. 13 (2011) R78, https://doi.org/10.1186/bcr2927.

[112] B. Lamas, R. Nachat-Kappes, N. Goncalves-Mendes, F. Mishellany, A. Rossary, M. P. Vasson, M.C. Farges, Dietary fat without body weight gain increases in vivo MCF-7 human breast cancer cell growth and decreases natural killer cell cytotoxicity, Mol. Carcinog. 54 (2015) 58–71, https://doi.org/10.1002/mc.22074.

[113] J.J. Melenhorst, G.M. Chen, M. Wang, D.L. Porter, C. Chen, M.A. Collins, P. Gao, S. Bandyopadhyay, H. Sun, Z. Zhao, S. Lundh, I. Pruteanu-Malinici, C.L. Nobles, S. Maji, N.V. Frey, S.I. Gill, L. Tian, I. Kulikovskaya, M. Gupta, D.E. Ambrose, M. M. Davis, J.A. Fraietta, J.L. Brogdon, R.M. Young, A. Chew, B.L. Levine, D. L. Siegel, C. Alanio, E.J. Wherry, F.D. Bushman, S.F. Lacey, K. Tan, C.H. June, Decade-long leukaemia remissions with persistence of CD4+ CAR T cells, Nature (2022), https://doi.org/10.1038/s41586-021-04390-6.

[114] A. Pfefferle, N.D. Huntington, You have got a fast CAR: chimeric antigen receptor NK cells in cancer therapy, Cancers 12 (2020), https://doi.org/10.3390/cancers12030706.

[115] Natural killer cells for cancer immunotherapy: a new CAR is catching up, EBioMedicine 39 (2019) 1–2, https://doi.org/10.1016/j.ebiom.2019.01.018.

[116] H. Klingemann, L. Boissel, F. Toneguzzo, Natural killer cells for immunotherapy - advantages of the NK-92 cell line over blood NK cells, Front. Immunol. 7 (2016), https://doi.org/10.3389/fimmu.2016.00091.

[117] G. Suck, M. Odendahl, P. Nowakowska, C. Seidl, W.S. Wels, H.G. Klingemann, T. Tonn, NK-92: an 'off-the-shelf therapeutic' for adoptive natural killer cell-based cancer immunotherapy, Cancer Immunol, Immunotherapy 65 (2016) 485–492, https://doi.org/10.1007/s00262-015-1761-x.

[118] H.G. Klingemann, E. Wong, G. Maki, A cytotoxic NK-cell line (NK-92) for ex vivo purging of leukemia from blood, Biol. Blood Marrow Transplant. 2 (1996) 68–75.

[119] S. Arai, R. Meagher, M. Swearingen, H. Myint, E. Rich, J. Martinson, H. Klingemann, Infusion of the allogeneic cell line NK-92 in patients with advanced renal cell cancer or melanoma: A phase I trial, Cytotherapy 10 (2008) 625–632, https://doi.org/10.1080/14653240802301872.

[120] T. Tonn, D. Schwabe, H.G. Klingemann, S. Becker, R. Esser, U. Koehl, M. Suttorp, E. Seifried, O.G. Ottmann, G. Bug, Treatment of patients with advanced cancer with the natural killer cell line NK-92, Cytotherapy 15 (2013) 1563–1570, https://doi.org/10.1016/j.jcyt.2013.06.017.

[121] M. Boyiadzis, M. Agha, R.L. Redner, A. Sehgal, A. Im, J.-Z. Hou, R. Farah, K. A. Dorritie, A. Raptis, S.H. Lim, H. Wang, N. Lapteva, Z. Mei, L.H. Butterfield, C. M. Rooney, T.L. Whiteside, Phase 1 clinical trial of adoptive immunotherapy using "off-the-shelf" activated natural killer cells in patients with refractory and relapsed acute myeloid leukemia, Cytotherapy 19 (2017) 1225–1232, https://doi.org/10.1016/j.jcyt.2017.07.008.

[122] B.A. Williams, A.D. Law, B. Routy, N. DenHollander, V. Gupta, X.-H. Wang, A. Chaboureau, S. Viswanathan, A. Keating, A phase I trial of NK-92 cells for refractory hematological malignancies relapsing after autologous hematopoietic cell transplantation shows safety and evidence of efficacy, Oncotarget 8 (2017) 89256–89268, https://doi.org/10.18632/oncotarget.19204.

[123] G. Xie, H. Dong, Y. Liang, J.D. Ham, R. Rizwan, J. Chen, CAR-NK cells: a promising cellular immunotherapy for cancer, EBioMedicine 59 (2020) 102975, https://doi.org/10.1016/j.ebiom.2020.102975.

[124] A. Yilmaz, H. Cui, M.A. Caligiuri, J. Yu, Chimeric antigen receptor-engineered natural killer cells for cancer immunotherapy, J. Hematol. Oncol. 13 (2020) 168, https://doi.org/10.1186/s13045-020-00998-9.

[125] N. Xia, P. Haopeng, J. Gong, J. Lu, Z. Chen, Y. Zheng, Z. Wang, Y. Sun, Z. Yang, R. M. Hoffman, F. Liu, Robo1-specific CAR-NK immunotherapy enhances efficacy of 125 I seed brachytherapy in an orthotopic mouse model of human pancreatic carcinoma, Anticancer Res. 39 (2019) 5919–5925, https://doi.org/10.21873/anticanres.13796.

[126] L. Chaojie, Y. Nannan, L. Huashun, W. Zhongmin, Robo1-specific chimeric antigen receptor natural killer cell therapy for pancreatic ductal adenocarcinoma with liver metastasis e, J. Cancer Res. Therapeut. 16 (2020) 393–396.

[127] K. Schönfeld, C. Sahm, C. Zhang, S. Naundorf, C. Brendel, M. Odendahl, P. Nowakowska, H. Bönig, U. Köhl, S. Kloess, S. Köhler, H. Holtgreve-Grez, A. Jauch, M. Schmidt, R. Schubert, K. Kühlcke, E. Seifried, H.G. Klingemann, M. A. Rieger, T. Tonn, M. Grez, W.S. Wels, Selective inhibition of tumor growth by clonal NK cells expressing an ErbB2/HER2-specific chimeric antigen receptor, Mol. Ther. 23 (2015) 330–338, https://doi.org/10.1038/mt.2014.219.

[128] R. Alkins, A. Burgess, M. Ganguly, G. Francia, R. Kerbel, W.S. Wels, K. Hynynen, Focused ultrasound delivers targeted immune cells to metastatic brain tumors, Cancer Res. 73 (2013) 1892–1899, https://doi.org/10.1158/0008-5472.CAN-12-2609.

[129] X. Wu, S. Huang, HER2-specific chimeric antigen receptor-engineered natural killer cells combined with apatinib for the treatment of gastric cancer, Bull. Cancer 106 (2019) 946–958, https://doi.org/10.1016/j.bulcan.2019.03.012.

[130] M. Yu, H. Luo, M. Fan, X. Wu, B. Shi, S. Di, Y. Liu, Z. Pan, H. Jiang, Z. Li, Development of GPC3-specific chimeric antigen receptor-engineered natural killer cells for the treatment of hepatocellular carcinoma, Mol. Ther. 26 (2018) 366–378, https://doi.org/10.1016/j.ymthe.2017.12.012.

[131] H. Tseng, W. Xiong, S. Badeti, Y. Yang, M. Ma, T. Liu, C.A. Ramos, G. Dotti, L. Fritzky, J. Jiang, Q. Yi, J. Guarrera, W.-X. Zong, C. Liu, D. Liu, Efficacy of anti-CD147 chimeric antigen receptors targeting hepatocellular carcinoma, Nat. Commun. 11 (2020) 4810, https://doi.org/10.1038/s41467-020-18444-2.

[132] C. Sahm, K. Schönfeld, W.S. Wels, Expression of IL-15 in NK cells results in rapid enrichment and selective cytotoxicity of gene-modiWed eVectors that carry a tumor-speciWc antigen receptor, Cancer Immunol. Immunother. 61 (2012) 1451–1461, https://doi.org/10.1007/s00262-012-1212-x.

[133] Q. Zhang, H. Zhang, J. Ding, H. Liu, H. Li, H. Li, M. Lu, Y. Miao, L. Li, J. Zheng, Combination therapy with EpCAM-CAR-NK-92 cells and regorafenib against human colorectal cancer models, J. Immunol. Res. (2018) 1–11, https://doi.org/10.1155/2018/4263520, 2018.

[134] X. Chen, J. Han, J. Chu, L. Zhang, J. Zhang, C. Chen, L. Chen, Y. Wang, H. Wang, L. Yi, J.B. Elder, Q.-E. Wang, X. He, B. Kaur, E.A. Chiocca, J. Yu, A combinational therapy of EGFR-CAR NK cells and oncolytic herpes simplex virus 1 for breast cancer brain metastases, Oncotarget 7 (2016) 27764–27777, https://doi.org/10.18632/oncotarget.8526.

[135] Z. Hu, Tissue factor as a new target for CAR-NK cell immunotherapy of triple-negative breast cancer, Sci. Rep. 10 (2020) 2815, https://doi.org/10.1038/s41598-020-59736-3.

[136] M. Kim, S. Pyo, C.H. Kang, C.O. Lee, H.K. Lee, S.U. Choi, C.H. Park, Folate receptor 1 (FOLR1) targeted chimeric antigen receptor (CAR) T cells for the treatment of gastric cancer, PLoS One 13 (2018), e0198347, https://doi.org/10.1371/journal.pone.0198347.

[137] C. Guo, E. Dong, Q. Lai, S. Zhou, G. Zhang, M. Wu, X. Yue, Y. Tao, Y. Peng, J. Ali, Y. Lu, Y. Fu, W. Lai, Z. Zhang, F. Ma, Y. Yao, L. Gou, H. Yang, J. Yang, Effective antitumor activity of 5T4-specific CAR-T cells against ovarian cancer cells in vitro and xenotransplanted tumors in vivo, MedComm 1 (2020) 338–350, https://doi.org/10.1002/mco2.34.

[138] Y.Y. Ng, Z. Du, X. Zhang, W.J. Chng, S. Wang, CXCR4 and anti-BCMA CAR co-modified natural killer cells suppress multiple myeloma progression in a xenograft mouse model, Cancer Gene Ther. (2021), https://doi.org/10.1038/s41417-021-00365-x.

[139] C. Jochems, J.W. Hodge, M. Fantini, R. Fujii, Y.M. Morillon, J.W. Greiner, M. R. Padget, S.R. Tritsch, K.Y. Tsang, K.S. Campbell, H. Klingemann, L. Boissel, S. Rabizadeh, P. Soon-Shiong, J. Schlom, An NK cell line (haNK) expressing high levels of granzyme and engineered to express the high affinity CD16 allele, Oncotarget 7 (2016) 86359–86373, https://doi.org/10.18632/oncotarget.13411.

[140] K.P. Fabian, M.R. Padget, R.N. Donahue, K. Solocinski, Y. Robbins, C.T. Allen, J. H. Lee, S. Rabizadeh, P. Soon-Shiong, J. Schlom, J.W. Hodge, PD-L1 targeting high-affinity NK (t-haNK) cells induce direct antitumor effects and target suppressive MDSC populations, J. Immunother. Cancer. 8 (2020), e000450, https://doi.org/10.1136/jitc-2019-000450.

[141] L. Xiao, D. Cen, H. Gan, Y. Sun, N. Huang, H. Xiong, Q. Jin, L. Su, X. Liu, K. Wang, G. Yan, T. Dong, S. Wu, P. Zhou, J. Zhang, W. Liang, J. Ren, Y. Teng, C. Chen, X. H. Xu, Adoptive transfer of NKG2D CAR mRNA-engineered natural killer cells in colorectal cancer patients, Mol. Ther. 27 (2019) 1114–1125, https://doi.org/10.1016/j.ymthe.2019.03.011.

[142] Y. Li, D. Hermanson, B. Moriarity, D. Kaufmann, Human iPSC-derived natural killer cells engineered with chimeric antigen receptors enhance anti-tumor activity, Stem Cell. 23 (2018) 181–192, https://doi.org/10.1016/j.stem.2018.06.002, e5.

[143] A. Leivas, A. Valeri, L. Córdoba, A. García-Ortiz, A. Ortiz, L. Sánchez-Vega, O. Graña-Castro, L. Fernández, G. Carreño-Tarragona, M. Pérez, D. Megías, M. L. Paciello, J. Sánchez-Pina, A. Pérez-Martínez, D.A. Lee, D.J. Powell, P. Río, J. Martínez-López, NKG2D-CAR-transduced natural killer cells efficiently target multiple myeloma, Blood Cancer J. 11 (2021) 146, https://doi.org/10.1038/s41408-021-00537-w.

[144] S. Yang, B. Cao, G. Zhou, L. Zhu, L. Wang, L. Zhang, H.F. Kwok, Z. Zhang, Q. Zhao, Targeting B7-H3 immune checkpoint with chimeric antigen receptor-engineered natural killer cells exhibits potent cytotoxicity against non-small cell lung cancer, Front. Pharmacol. 11 (2020), https://doi.org/10.3389/fphar.2020.01089.

[145] H. Walczak, R.E. Miller, K. Ariail, B. Gliniak, T.S. Griffith, M. Kubin, W. Chin, J. Jones, A. Woodward, T. Le, C. Smith, P. Smolak, R.G. Goodwin, C.T. Rauch, J.C. L. Schuh, D.H. Lynch, Tumoricidal activity of tumor necrosis factor–related apoptosis–inducing ligand in vivo, Nat. Med. 5 (1999) 157–163, https://doi.org/10.1038/5517.

[146] X. Song, S.-H. Hong, W.T. Kwon, L.M. Bailey, P. Basse, D.L. Bartlett, Y.T. Kwon, Y. J. Lee, Secretory TRAIL-armed natural killer cell–based therapy: in vitro and in vivo colorectal peritoneal carcinomatosis xenograft, Mol. Cancer Therapeut. 15 (2016) 1591–1601, https://doi.org/10.1158/1535-7163.MCT-15-0937.

[147] Z. Wang, L. Guo, Y. Song, Y. Zhang, D. Lin, B. Hu, Y. Mei, D. Sandikin, H. Liu, Augmented anti-tumor activity of NK-92 cells expressing chimeric receptors of TGF-βR II and NKG2D, Cancer Immunol. Immunother. 66 (2017) 537–548, https://doi.org/10.1007/s00262-017-1959-1.

[148] R. Bjordahl, S. Gaidarova, J.P. Goodridge, S. Mahmood, G. Bonello, M. Robinson, C. Ruller, M. Pribadi, T. Lee, R. Abujarour, J. Dinella, J. Huffman, H. Chu, U. Hopken, A. Rehm, B. Valamehr, FT576: a novel multiplexed engineered off-the-shelf natural killer cell immunotherapy for the dual-targeting of CD38 and bcma for the treatment of multiple myeloma, Blood 134 (2019), https://doi.org/10.1182/blood-2019-131373, 3214–3214.

[149] J.P. Goodridge, R. Bjordahl, S. Mahmood, J. Reiser, S. Gaidarova, R. Blum, F. Cichocki, H. Chu, G. Bonello, T. Lee, B. Groff, M. Meza, Y.-W. Chu, B. Walcheck, K.-J. Malmberg, J.S. Miller, A. Rehm, U. Hopken, B. Valamehr, FT576: multi-specific off-the-shelf CAR-NK cell therapy engineered for enhanced persistence, avoidance of self-fratricide and optimized mab combination therapy to prevent antigenic escape and elicit a deep and durable response in multiple myeloma, Blood 136 (2020) 4–5, https://doi.org/10.1182/blood-2020-142750.

[150] X. Tang, L. Yang, Z. Li, A.P. Nalin, H. Dai, T. Xu, J. Yin, F. You, M. Zhu, W. Shen, G. Chen, X. Zhu, D. Wu, J. Yu, First-in-man clinical trial of CAR NK-92 cells: safety test of CD33-CAR NK-92 cells in patients with relapsed and refractory acute myeloid leukemia, Am. J. Cancer Res. 8 (2018) 1083–1089, 2018;8(6):1083-1089.

[151] E. Liu, D. Marin, P. Banerjee, H.A. Macapinlac, P. Thompson, R. Basar, L. Nassif Kerbauy, B. Overman, P. Thall, M. Kaplan, V. Nandivada, I. Kaur, A. Nunez Cortes, K. Cao, M. Daher, C. Hosing, E.N. Cohen, P. Kebriaei, R. Mehta, S. Neelapu, Y. Nieto, M. Wang, W. Wierda, M. Keating, R. Champlin, E.J. Shpall, K. Rezvani, Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors, N. Engl. J. Med. 382 (2020) 545–553, https://doi.org/10.1056/NEJMoa1910607.

[152] P. Sharma, J.P. Allison, Leading edge review immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential, Cell 161 (2015) 205–214, https://doi.org/10.1016/j.cell.2015.03.030.

[153] B.A. Wilky, Immune checkpoint inhibitors: the linchpins of modern immunotherapy, Immunol. Rev. 290 (2019) 6–23, https://doi.org/10.1111/imr.12766.

[154] J. Hsu, J.J. Hodgins, M. Marathe, C.J. Nicolai, M.C. Bourgeois-Daigneault, T. N. Trevino, C.S. Azimi, A.K. Scheer, H.E. Randolph, T.W. Thompson, L. Zhang, A. Iannello, N. Mathur, K.E. Jardine, G.A. Kirn, J.C. Bell, M.W. McBurney, D. H. Raulet, M. Ardolino, Contribution of NK cells to immunotherapy mediated by PD-1/PD-L1 blockade, J. Clin. Invest. 128 (2018) 4654–4668, https://doi.org/10.1172/JCI99317.

[155] Y. Liu, Y. Cheng, Y. Xu, Z. Wang, X. Du, C. Li, J. Peng, L. Gao, X. Liang, C. Ma, Increased expression of programmed cell death protein 1 on NK cells inhibits NK-cell-mediated anti-tumor function and indicates poor prognosis in digestive cancers, Oncogene 36 (2017) 6143–6153, https://doi.org/10.1038/onc.2017.209.

[156] P. André, C. Denis, C. Soulas, C. Bourbon-Caillet, J. Lopez, T. Arnoux, M. Bléry, C. Bonnafous, L. Gauthier, A. Morel, B. Rossi, R. Remark, V. Breso, E. Bonnet, G. Habif, S. Guia, A.I. Lalanne, C. Hoffmann, O. Lantz, J. Fayette, A. Boyer-Chammard, R. Zerbib, P. Dodion, H. Ghadially, M. Jure-Kunkel, Y. Morel, R. Herbst, E. Narni-Mancinelli, R.B. Cohen, E. Vivier, Anti-NKG2A mAb is a checkpoint inhibitor that promotes anti-tumor immunity by unleashing both T and NK cells, Cell 175 (2018) 1731–1743, https://doi.org/10.1016/j.cell.2018.10.014, e13.

[157] C. Sun, J. Xu, Q. Huang, M. Huang, H. Wen, C. Zhang, J. Wang, J. Song, M. Zheng, H. Sun, H. Wei, W. Xiao, R. Sun, Z. Tian, High NKG2A expression contributes to NK cell exhaustion and predicts a poor prognosis of patients with liver cancer, OncoImmunology 6 (2017), e1264562, https://doi.org/10.1080/2162402X.2016.1264562.

[158] C. Bossard, S. Bézieau, T. Matysiak-Budnik, C. Volteau, C.L. Laboisse, F. Jotereau, J.-F. Mosnier, HLA-E/β2 microglobulin overexpression in colorectal cancer is associated with recruitment of inhibitory immune cells and tumor progression, Int. J. Cancer 131 (2012) 855–863, https://doi.org/10.1002/ijc.26453.

[159] Y. Chen, Z. Xin, L. Huang, L. Zhao, S. Wang, J. Cheng, P. Wu, Y. Chai, CD8+ T cells form the predominant subset of NKG2A+ cells in human lung cancer, Front. Immunol. 10 (2020), https://doi.org/10.3389/fimmu.2019.03002.

[160] T. Kamiya, S.V. Seow, D. Wong, M. Robinson, D. Campana, Blocking expression of inhibitory receptor NKG2A overcomes tumor resistance to NK cells, J. Clin. Invest. 129 (2019) 2094–2106, https://doi.org/10.1172/JCI123955.

[161] A.V. Tinker, H.W. Hirte, D. Provencher, M. Butler, H. Ritter, D. Tu, H.A. Azim, P. Paralejas, N. Grenier, S.-A. Hahn, J. Ramsahai, L. Seymour, Dose-ranging and cohort-expansion study of monalizumab (IPH2201) in patients with advanced gynecologic malignancies: a trial of the Canadian cancer trials group (CCTG): IND221, Clin. Cancer Res. 25 (2019) 6052–6060, https://doi.org/10.1158/1078-0432.CCR-19-0298.

[162] N.H. Segal, J. Naidoo, G. Curigliano, S. Patel, S. Sahebjam, K.P. Papadopoulos, M. S. Gordon, D. Wang, A. Gómez Rueda, X. Song, X. Li, S. Marshall, S.E. Abdullah, J. R. Diamond, First-in-human dose escalation of monalizumab plus durvalumab, with expansion in patients with metastatic microsatellite-stable colorectal cancer, J. Clin. Oncol. 36 (2018), https://doi.org/10.1200/jco.2018.36.15_suppl.3540, 3540–3540.

[163] T.A. Waldmann, Interleukin-15 in the treatment of cancer, Expet Rev. Clin. Immunol. 10 (2014) 1689–1701, https://doi.org/10.1586/1744666X.2014.973856.

[164] T.A. Waldmann, The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design, Nat. Rev. Immunol. 6 (2006) 595–601, https://doi.org/10.1038/nri1901.

[165] Y. Yang, A. Lundqvist, Immunomodulatory effects of IL-2 and IL-15; implications for cancer immunotherapy, Cancers 12 (2020), https://doi.org/10.3390/cancers12123586.

[166] K.M. Knudson, J.W. Hodge, J. Schlom, S.R. Gameiro, Rationale for IL-15 superagonists in cancer immunotherapy, Expet Opin. Biol. Ther. 20 (2020) 705–709, https://doi.org/10.1080/14712598.2020.1738379.

[167] Y. Chen, B. Chen, T. Yang, W. Xiao, L. Qian, Y. Ding, M. Ji, X. Ge, W. Gong, Human fused NKG2D-IL-15 protein controls xenografted human gastric cancer through the recruitment and activation of NK cells, Cell. Mol. Immunol. 14 (2017) 293–307, https://doi.org/10.1038/cmi.2015.81.

[168] M. Felices, S. Chu, B. Kodal, L. Bendzick, C. Ryan, A.J. Lenvik, K.L.M. Boylan, H. C. Wong, A.P.N. Skubitz, J.S. Miller, M.A. Geller, IL-15 super-agonist (ALT-803) enhances natural killer (NK) cell function against ovarian cancer, Gynecol. Oncol. 145 (2017) 453–461, https://doi.org/10.1016/j.ygyno.2017.02.028.

[169] P.S. Kim, A.R. Kwilas, W. Xu, S. Alter, E.K. Jeng, H.C. Wong, J. Schlom, J. W. Hodge, IL-15 superagonist/IL-15RαSushi-Fc fusion complex (IL-15SA/IL-15RαSu-Fc; ALT-803) markedly enhances specific subpopulations of NK and memory CD8+ T cells, and mediates potent anti-tumor activity against murine breast and colon carcinomas, Oncotarget 7 (2016) 16130–16145, https://doi.org/10.18632/oncotarget.7470.

[170] R. Romee, S.E. Schneider, J.W. Leong, J.M. Chase, C.R. Keppel, R.P. Sullivan, M. A. Cooper, T.A. Fehniger, Cytokine activation induces human memory-like NK cells, Blood 120 (2012) 4751–4760, https://doi.org/10.1182/blood-2012-04-419283.

[171] R. Romee, M. Rosario, M.M. Berrien-Elliott, J.A. Wagner, B.A. Jewell, T. Schappe, J.W. Leong, S. Abdel-Latif, S.E. Schneider, S. Willey, C.C. Neal, L. Yu, S.T. Oh, Y.-S. Lee, A. Mulder, F. Claas, M.A. Cooper, T.A. Fehniger, Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia, Sci. Transl. Med. 8 (2016), https://doi.org/10.1126/scitranslmed.aaf2341, 357ra123.

[172] L.D. Uppendahl, M. Felices, L. Bendzick, C. Ryan, B. Kodal, P. Hinderlie, K.L. M. Boylan, A.P.N. Skubitz, J.S. Miller, M.A. Geller, Cytokine-induced memory-like natural killer cells have enhanced function, proliferation, and in vivo expansion against ovarian cancer cells, Gynecol. Oncol. 153 (2019) 149–157, https://doi.org/10.1016/j.ygyno.2019.01.006.

[173] N. Kedia-Mehta, L. Tobin, V. Zaiatz-Bittencourt, M.M. Pisarska, C. De Barra, C. Choi, E. Elamin, D. O'Shea, C.M. Gardiner, D.K. Finlay, A.E. Hogan, Cytokine-induced natural killer cell training is dependent on cellular metabolism and is defective in obesity, Blood Adv 5 (2021) 4447–4455, https://doi.org/10.1182/bloodadvances.2021005047.

[174] C.G. Drake, Combination immunotherapy approaches, Ann. Oncol. 23 (2012) viii41–viii46, https://doi.org/10.1093/annonc/mds262.

[175] S.-E. Bentebibel, M.E. Hurwitz, C. Bernatchez, C. Haymaker, C.W. Hudgens, H. M. Kluger, M.T. Tetzlaff, M.A. Tagliaferri, J. Zalevsky, U. Hoch, C. Fanton, S. Aung, P. Hwu, B.D. Curti, N.M. Tannir, M. Sznol, A. Diab, A first-in-human study and biomarker analysis of NKTR-214, a novel IL2Rβγ-biased cytokine, in patients with advanced or metastatic solid tumors, Cancer Discov. 9 (2019) 711–721, https://doi.org/10.1158/2159-8290.CD-18-1495.

[176] M. Sharma, H. Khong, F. Fa'ak, S.-E. Bentebibel, L.M.E. Janssen, B.C. Chesson, C. A. Creasy, M.-A. Forget, L.M.S. Kahn, B. Pazdrak, B. Karki, Y. Hailemichael, M. Singh, C. Vianden, S. Vennam, U. Bharadwaj, D.J. Tweardy, C. Haymaker, C. Bernatchez, S. Huang, K. Rajapakshe, C. Coarfa, M.E. Hurwitz, M. Sznol, P. Hwu, U. Hoch, M. Addepalli, D.H. Charych, J. Zalevsky, A. Diab, W. W. Overwijk, Bempegaldesleukin selectively depletes intratumoral Tregs and potentiates T cell-mediated cancer therapy, Nat. Commun. 11 (2020) 661, https://doi.org/10.1038/s41467-020-14471-1.

[177] S.E. Bentebibel, M.E. Hurwitz, C. Bernatchez, C. Haymaker, C.W. Hudgens, H. M. Kluger, M.T. Tetzlaff, M.A. Tagliaferri, J. Zalevsky, U. Hoch, C. Fanton, S. Aung, P. Hwu, B.D. Curti, N.M. Tannir, M. Sznol, A. Diab, A first-in-human study and biomarker analysis of NKTR-214, a novel IL2Rβγ-biased cytokine, in patients with advanced or metastatic solid tumors, Cancer Discov. 9 (2019) 711–721, https://doi.org/10.1158/2159-8290.CD-18-1495.

[178] A. Diab, N.M. Tannir, S.-E. Bentebibel, P. Hwu, V. Papadimitrakopoulou, C. Haymaker, H.M. Kluger, S.N. Gettinger, M. Sznol, S.S. Tykodi, B.D. Curti, M. A. Tagliaferri, J. Zalevsky, A.L. Hannah, U. Hoch, S. Aung, C. Fanton, A. Rizwan, E. Iacucci, Y. Liao, C. Bernatchez, M.E. Hurwitz, D.C. Cho, Bempegaldesleukin (NKTR-214) plus nivolumab in patients with advanced solid tumors: phase I dose-escalation study of safety, efficacy, and immune activation (PIVOT-02), Cancer Discov. 10 (2020) 1158 LP–1173, https://doi.org/10.1158/2159-8290.CD-19-1510.

[179] C. Xu, D. Liu, Z. Chen, F. Zhuo, H. Sun, J. Hu, T. Li, Umbilical cord blood–derived natural killer cells combined with bevacizumab for colorectal cancer treatment, Hum. Gene Ther. 30 (2019) 459–470, https://doi.org/10.1089/hum.2018.011.

[180] T.E. Seery, M. Kistler, L.S. Sender, J.H. Lee, A.M. Shinde, A. Annamalai, P. Soon-Shiong, Innate and adaptive immunotherapy: an orchestration of immunogenic cell death by overcoming immune suppression and activating NK and T cell therapy in patients with third line or greater metastatic pancreatic cancer, J. Clin. Oncol. 37 (2019), https://doi.org/10.1200/JCO.2019.37.15_suppl.e15787 e15787–e15787.

[181] NantKwest, ImmunityBio, NantKwest and ImmunityBio Present Results of Landmark Trial of First-In-Human Natural Killer Cell Combination Immunotherapy with Durable, Complete Response Data and 78% Disease Control in Refractory Triple Negative Breast Cancer at SABCS, 2019. https://ir.immunitybio.com/news-releases/news-release-details/nantkwest-and-immunitybio-present-results-landmark-trial-first?field_nir_news_date_value%5Bmin%5D=. (Accessed 1 November 2021).

[182] NantKwest, ImmunityBio, NantKwest, ImmunityBio Announce Positive Interim Data on Survival Rates in Metastatic Pancreatic Cancer Trials | Business Wire, 2021. https://www.businesswire.com/news/home/20210113005928/en/Nant

Kwest-ImmunityBio-Announce-Positive-Interim-Data-on-Survival-Rates-in-Metastatic-Pancreatic-Cancer-Trials. (Accessed 1 November 2021).
[183] L. Tan, S. Han, S. Ding, W. Xiao, Y. Ding, L. Qian, C. Wang, W. Gong, Chitosan nanoparticle-based delivery of fused NKG2D-IL-21 gene suppresses colon cancer growth in mice, Int. J. Nanomed. 12 (2017) 3095–3107, https://doi.org/10.2147/IJN.S128032.
[184] N. Nagarsheth, M.S. Wicha, W. Zou, Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy, Nat. Rev. Immunol. 17 (2017) 559–572, https://doi.org/10.1038/nri.2017.49.
[185] M.T. Chow, A.D. Luster, Chemokines in cancer, Cancer Immunol. Res. 2 (2014) 1125–1131, https://doi.org/10.1158/2326-6066.CIR-14-0160.
[186] P.P.C. Wong, A. Kariminia, D. Jones, C.J. Eaves, R. Foley, S. Ivison, S. Couban, K. R. Schultz, Plerixafor effectively mobilizes CD56bright NK cells in blood, providing an allograft predicted to protect against GVHD, Blood 131 (2018) 2863–2865, https://doi.org/10.1182/blood-2018-03-836700.
[187] D. Biasci, M. Smoragiewicz, C.M. Connell, Z. Wang, Y. Gao, J.E.D. Thaventhiran, B. Basu, L. Magiera, T.I. Johnson, L. Bax, A. Gopinathan, C. Isherwood, F. A. Gallagher, M. Pawula, I. Hudecova, D. Gale, N. Rosenfeld, P. Barmpounakis, E. C. Popa, R. Brais, E. Godfrey, F. Mir, F.M. Richards, D.T. Fearon, T. Janowitz, D. I. Jodrell, CXCR4 inhibition in human pancreatic and colorectal cancers induces an integrated immune response, Proc. Natl. Acad. Sci. Unit. States Am. 117 (2020) 28960–28970, https://doi.org/10.1073/pnas.2013644117.
[188] B. Bockorny, V. Semenisty, T. Macarulla, E. Borazanci, B.M. Wolpin, S. M. Stemmer, T. Golan, R. Geva, M.J. Borad, K.S. Pedersen, J.O. Park, R. A. Ramirez, D.G. Abad, J. Feliu, A. Muñoz, M. Ponz-Sarvise, A. Peled, T.M. Lustig, O. Bohana-Kashtan, S.M. Shaw, E. Sorani, M. Chaney, S. Kadosh, A. Vainstein Haras, D.D. Von Hoff, M. Hidalgo, BL-8040, a CXCR4 antagonist, in combination with pembrolizumab and chemotherapy for pancreatic cancer: the COMBAT trial, Nat. Med. 26 (2020) 878–885, https://doi.org/10.1038/s41591-020-0880-x.
[189] M.H. O'Hara, W. Messersmith, H. Kindler, W. Zhang, C. Pitou, A.M. Szpurka, D. Wang, S.-B. Peng, B. Vangerow, A.A. Khan, M. Koneru, A. Wang-Gillam, Safety and pharmacokinetics of CXCR4 peptide antagonist, LY2510924, in combination with durvalumab in advanced refractory solid tumors, J. Pancreat. Cancer. 6 (2020) 21–31, https://doi.org/10.1089/pancan.2019.0018.
[190] N. Halama, I. Zoernig, A. Berthel, C. Kahlert, F. Klupp, M. Suarez-Carmona, T. Suetterlin, K. Brand, J. Krauss, F. Lasitschka, T. Lerchl, C. Luckner-Minden, A. Ulrich, M. Koch, J. Weitz, M. Schneider, M.W. Buechler, L. Zitvogel, T. Herrmann, A. Benner, C. Kunz, S. Luecke, C. Springfeld, N. Grabe, C.S. Falk, D. Jaeger, Tumoral immune cell exploitation in colorectal cancer metastases can Be targeted effectively by anti-CCR5 therapy in cancer patients, Cancer Cell 29 (2016) 587–601, https://doi.org/10.1016/j.ccell.2016.03.005.
[191] M.J. Conroy, K.C. Galvin, M.E. Kavanagh, A.M. Mongan, S.L. Doyle, N. Gilmartin, C. O'Farrelly, J.V. Reynolds, J. Lysaght, CCR1 antagonism attenuates T cell trafficking to omentum and liver in obesity-associated cancer, Immunol. Cell Biol. 94 (2016) 531–537, https://doi.org/10.1038/icb.2016.26.
[192] V. Kremer, M.A. Ligtenberg, R. Zendehdel, C. Seitz, A. Duivenvoorden, E. Wennerberg, E. Colón, A.-H. Scherman-Plogell, A. Lundqvist, Genetic engineering of human NK cells to express CXCR2 improves migration to renal cell carcinoma, J. Immunother. Cancer. 5 (2017) 73, https://doi.org/10.1186/s40425-017-0275-9.
[193] M. Carlsten, E. Levy, A. Karambelkar, L. Li, R. Reger, M. Berg, M.V. Peshwa, R. W. Childs, Efficient mRNA-based genetic engineering of human NK cells with high-affinity CD16 and CCR7 augments rituximab-induced ADCC against lymphoma and targets NK cell migration toward the lymph node-associated chemokine CCL19, Front. Immunol. 7 (2016) 105, https://doi.org/10.3389/fimmu.2016.00105.
[194] E. Levy, R. Reger, F. Segerberg, M. Lambert, C. Leijonhufvud, Y. Baumer, M. Carlsten, R. Childs, Enhanced bone marrow homing of natural killer cells following mRNA transfection with gain-of-function variant CXCR4R334X, Front. Immunol. 10 (2019), https://doi.org/10.3389/fimmu.2019.01262.
[195] K.-S. Kim, J.-H. Han, S.H. Choi, H.-Y. Jung, J.D. Park, H.-J. An, S.-E. Kim, D.-H. Kim, J. Doh, D.K. Han, I.-H. Kim, W. Park, K.-S. Park, Cationic nanoparticle-mediated activation of natural killer cells for effective cancer immunotherapy, ACS Appl. Mater. Interfaces 12 (2020) 56731–56740, https://doi.org/10.1021/acsami.0c16357.
[196] S.S. Somanchi, A. Somanchi, L.J.N. Cooper, D.A. Lee, Engineering lymph node homing of ex vivo-expanded human natural killer cells via trogocytosis of the chemokine receptor CCR7, Blood 119 (2012) 5164–5172, https://doi.org/10.1182/blood-2011-11-389924.
[197] E. Wennerberg, V. Kremer, R. Childs, A. Lundqvist, CXCL10-induced migration of adoptively transferred human natural killer cells toward solid tumors causes regression of tumor growth in vivo, Cancer Immunol. Immunother. 64 (2015) 225–235, https://doi.org/10.1007/s00262-014-1629-5.
[198] Y.Y. Ng, J.C.K. Tay, S. Wang, CXCR1 expression to improve anti-cancer efficacy of intravenously injected CAR-NK cells in mice with peritoneal xenografts, Mol. Ther. - Oncolytics. 16 (2020) 75–85, https://doi.org/10.1016/j.omto.2019.12.006.
[199] N. Müller, S. Michen, S. Tietze, K. Töpfer, A. Schulte, K. Lamszus, M. Schmitz, G. Schackert, I. Pastan, A. Temme, Engineering NK cells modified with an EGFRvIII-specific chimeric antigen receptor to overexpress CXCR4 improves immunotherapy of CXCL12/SDF-1α-secreting glioblastoma, J. Immunother. 38 (2015) 197–210, https://doi.org/10.1097/CJI.0000000000000082.
[200] F. Li, Y. Sheng, W. Hou, P. Sampath, D. Byrd, S. Thorne, Y. Zhang, CCL5-armed oncolytic virus augments CCR5-engineered NK cell infiltration and antitumor efficiency, J. Immunother. Cancer. 8 (2020), e000131, https://doi.org/10.1136/jitc-2019-000131.
[201] E. Pérez del Río, F. Santos, X. Rodriguez Rodriguez, M. Martínez-Miguel, R. Roca-Pinilla, A. Arís, E. Garcia-Fruitós, J. Veciana, J.P. Spatz, I. Ratera, J. Guasch, CCL21-loaded 3D hydrogels for T cell expansion and differentiation, Biomaterials 259 (2020), 120313, https://doi.org/10.1016/j.biomaterials.2020.120313.
[202] C. Zheng, Q. Wang, Y. Wang, X. Zhao, K. Gao, Q. Liu, Y. Zhao, Z. Zhang, Y. Zheng, J. Cao, H. Chen, L. Shi, C. Kang, Y. Liu, Y. Lu, In situ modification of the tumor cell surface with immunomodulating nanoparticles for effective suppression of tumor growth in mice, Adv. Mater. 31 (2019), 1902542, https://doi.org/10.1002/adma.201902542.
[203] D. Peng, I. Kryczek, N. Nagarsheth, L. Zhao, S. Wei, W. Wang, Y. Sun, E. Zhao, L. Vatan, W. Szeliga, J. Kotarski, R. Tarkowski, Y. Dou, K. Cho, S. Hensley-Alford, A. Munkarah, R. Liu, W. Zou, Epigenetic silencing of TH1-type chemokines shapes tumour immunity and immunotherapy, Nature 527 (2015) 249–253, https://doi.org/10.1038/nature15520.
[204] F. Vahedi, T. Nham, S.M. Poznanski, M.V. Chew, M.M. Shenouda, D. Lee, A. A. Ashkar, Ex vivo expanded human NK cells survive and proliferate in humanized mice with autologous human immune cells, Sci. Rep. 7 (2017) 12083, https://doi.org/10.1038/s41598-017-12223-8.
[205] M. Gurney, S. Kundu, S. Pandey, M. O'Dwyer, Feeder cells at the interface of natural killer cell activation, expansion and gene editing, Front. Immunol. 13 (2022), https://doi.org/10.3389/fimmu.2022.802906.
[206] M.J. Conroy, M.R. Dunne, C.L. Donohoe, J.V. Reynolds, Obesity-associated cancer: an immunological perspective, Proc. Nutr. Soc. 75 (2016) 125–138, https://doi.org/10.1017/S0029665115004176.
[207] A. Lautenbach, C.D. Wrann, R. Jacobs, G. Müller, G. Brabant, H. Nave, Altered phenotype of NK cells from obese rats can Be normalized by transfer into lean animals, Obesity 17 (2009) 1848–1855, https://doi.org/10.1038/oby.2009.140.
[208] K.C. Galvin, M.J. Conroy, S.L. Doyle, M.R. Dunne, R. Fahey, E. Foley, K. E. O'Sullivan, D.G. Doherty, J.G. Geoghegan, N. Ravi, C. O'Farrelly, J. V. Reynolds, J. Lysaght, Extratumoral PD-1 blockade does not perpetuate obesity-associated inflammation in esophageal adenocarcinoma, Cancer Lett. 418 (2018) 230–238, https://doi.org/10.1016/j.canlet.2018.01.039.
[209] A. Cortellini, M. Bersanelli, S. Buti, K. Cannita, D. Santini, F. Perrone, R. Giusti, M. Tiseo, M. Michiara, P. Di Marino, N. Tinari, M. De Tursi, F. Zoratto, E. Veltri, R. Marconcini, F. Malorgio, M. Russano, C. Anesi, T. Zeppola, M. Filetti, P. Marchetti, A. Botticelli, G.C. Antonini Cappellini, F. De Galitiis, M.G. Vitale, F. Rastelli, F. Pergolesi, R. Berardi, S. Rinaldi, M. Tudini, R.R. Silva, A. Pireddu, F. Atzori, R. Chiari, B. Ricciuti, A. De Giglio, D. Iacono, A. Gelibter, M. A. Occhipinti, A. Parisi, G. Porzio, M.C. Fargnoli, P.A. Ascierto, C. Ficorella, C. Natoli, A multicenter study of body mass index in cancer patients treated with anti-PD-1/PD-L1 immune checkpoint inhibitors: when overweight becomes favorable, J. Immunother. Cancer. 7 (2019) 57, https://doi.org/10.1186/s40425-019-0527-y.
[210] M.E. Kavanagh, M.J. Conroy, N.E. Clarke, N.T. Gilmartin, R. Feighery, F. MacCarthy, D. O'Toole, N. Ravi, J.V. Reynolds, J. O' Sullivan, J. Lysaght, Altered T cell migratory capacity in the progression from Barrett oesophagus to oesophageal adenocarcinoma, Cancer Microenviron. (2019), https://doi.org/10.1007/s12307-019-00220-6.
[211] M.I. Palacios-Arreola, K.E. Nava-Castro, J.I. Castro, E. García-Zepeda, J. C. Carrero, J. Morales-Montor, The role of chemokines in breast cancer pathology and its possible use as therapeutic targets, J. Immunol. Res. (2014), 849720, https://doi.org/10.1155/2014/849720, 2014.
[212] B. Vicinus, C. Rubie, N. Stegmaier, V.O. Frick, K. Kölsch, A. Kauffels, P. Ghadjar, M. Wagner, M. Glanemann, miR-21 and its target gene CCL20 are both highly overexpressed in the microenvironment of colorectal tumors: significance of their regulation, Oncol. Rep. 30 (2013) 1285–1292, https://doi.org/10.3892/or.2013.2580.
[213] J. Huang, Z. Chen, C. Ding, S. Lin, D. Wan, K. Ren, Prognostic biomarkers and immunotherapeutic targets among CXC chemokines in pancreatic adenocarcinoma, Front. Oncol. 11 (2021), https://doi.org/10.3389/fonc.2021.711402.