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Obesity-associated cancer: an immunological perspective

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Epidemiological studies have established an association between obesity, insulin resistance, type 2 diabetes and a number of cancer types. Research has focused predominantly on altered endocrine factors, growth factors and signalling pathways, with little known in man about the immune involvement in the relevant pathophysiological processes. Moreover, in an era of exciting new breakthroughs in cancer immunotherapy, there is also a need to study the safety and efficacy of immunotherapeutics in the complex setting of inflammatory-driven obesity-associated cancer. This review addresses key immune cell subsets underpinning obesity-associated inflammation and describes how such immune compartments might be targeted to prevent and treat obesity-associated cancer. We propose that the modulation, metabolism, migration and abundance of pro- and anti-inflammatory cells and tumour-specific T cells might be therapeutically altered to both restore immune balance, alleviating pathological inflammation, and to improve anti-tumour immune responses in obesity-associated cancer.

Obesity: Cancer: Lymphocytes: Immunotherapeutics: Inflammation

The burgeoning global health burden of obesity is of grave concern, affecting over half a billion adults worldwide, with approximately 3.5 million attributable deaths each year⁽¹⁾. Despite national and international interventions to promote a healthy diet and lifestyle, recent reports predict that global obesity rates show no signs of abating, with predictions that half of all adults will be overweight or obese by 2030 (WHO). The worldwide prevalence of obesity almost doubled in the period 1980–2008. In 1980, 5 % of men and 8 % of women were obese and by 2008, these rates were 10 and 14 %, respectively. In many areas of the western world, the overweight phenotype is now the most prevalent body type. For example, in the USA in 2010 the prevalence of a BMI \geq 25 was 69.2 %, with 35.9 % of people being obese (BMI \geq 30)⁽²⁾. A cause of current concern is that more than one-third of children are overweight or obese in the USA, with adolescent obesity rates quadrupling over the past 30 years⁽³⁾. WHO figures also show that one in three European children are overweight or obese and of these, 60 % are predicted to be obese in adulthood⁽¹⁾.

Obesity may fuel pathological chronic inflammation and therefore a substantial proportion of adults and children worldwide are at risk of developing obesity-associated morbidities such as cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), non-alcoholic steatohepatitis and cancer^(1,4–7). Obesity contributes to between 3 and 20 % of cancer deaths in western populations^(8,9). Since obesity is a pro-inflammatory state, an altered immune system may fuel this process, with visceral adipose tissue and liver being primary sources of cells and cytokines. Understanding the role of obesity and related metabolic syndrome, insulin resistance, and T2DM in carcinogenesis and tumour biology is consequently the focus of significant present research interest, with most lessons learned from experimental models but with an increasing focus on studies in human subjects. In an era of novel immunotherapeutics in cancer, when targeted therapies such as nivolumab and ipilimumab have shown promise for several tumour types, a greater understanding in man of the impact of such approaches on obesity-associated cancers is required⁽¹⁰⁾. Such cancers

Abbreviations: IFN, interferon; IGF, insulin-like growth factor; iNKT, invariant natural killer T cells; MAIT, mucosal associated invariant T cells; NK, natural killer; OxPhos, oxidative phosphorylation; T2DM, type 2 diabetes mellitus; Th1, Th2, Th17 and T_{reg}, T helper type 1, 2 and 17 and regulatory T cells respectively; VAT, visceral adipose tissue.

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Table 1. Hazard ratio (HR) for cancers per 5 kg/m² increase in BMI⁽¹²⁾

Site	HR	CI	P-value
Colon	1.1	1.07, 1.13	<0.0001
Rectum	1.04	1.0, 1.08	0.017
Liver	1.19	1.12, 1.27	<0.0001
Gallbladder	1.31	1.12, 1.52	<0.0001
Pancreas	1.05	1.0, 1.1	0.012
Breast (post-menopausal)	1.05	1.03, 1.07	<0.0001
Cervix	1.1	1.03, 1.17	<0.0001
Ovary	1.09	1.04, 1.14	<0.0001
Uterus	1.62	1.56, 1.69	<0.0001
Kidney	1.25	1.17, 1.33	<0.0001
Thyroid	1.09	1.00, 1.19	0.0088
Leukaemia	1.09	1.05, 1.13	<0.0001

represent a unique immunotherapeutic challenge because an enhanced T helper type 1 (Th1) immune response is required to augment anti-tumour immunity, but without exacerbating tumourigenic obesity-associated inflammation⁽¹⁰⁾. Herein, we address the pathophysiological processes driving obesity-associated inflammation with a focus on both the innate and adaptive arms of the immune system, and discuss future prospects for treatment of obesity-associated malignancy.

Epidemiology

The epidemiological evidence underpinning the association between obesity and cancer incidence is now compelling. Large population-based prospective studies have demonstrated convincingly consistent increased cancer incidences per 5 kg/m² increase in BMI^(4,8,11–13). For example, a recent UK population based prospective cohort of 5.2 million patients with a median follow-up of 6 years recorded 166 966 incident cancers across twenty-two of the most common cancers⁽¹²⁾. BMI was positively associated with cancers at the following sites: colon, rectum, liver, gallbladder, pancreas, breast (post-menopausal only), cervix, ovary, uterus, kidney, thyroid and leukaemia⁽¹²⁾. The derived hazard ratios from this study are displayed in Table 1. The administrative dataset used in this study was unable to subtype cancers, for example both squamous and adenocarcinomas of the oesophagus were pooled as oesophageal cancer. This probably accounts for the lack of association between oesophageal adenocarcinoma and obesity, which has been consistent and marked in other studies (approximate hazard ratios 4.76, 95 % CI 2.96, 7.66; for patients with BMI \geq 40 compared with normal BMI)^(8,14). A meta-analysis prospective study of 282 000 cancer cases from population of 4.8 million patients demonstrated similarly consistent findings across disease sites and sexes⁽⁸⁾. Applying the Bradford-Hill hypotheses of strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy, obesity is a strong candidate to be a causal factor in the development of cancer as detailed in a review by Renehan *et al.*^(15,16).

Further epidemiological studies may lead to refinement of the associated increases in relative risk of incident cancers, especially cancers at sites with a less frequent incidence. Current estimates are subject to wide CI at disease sites where few incident cancers are reported. Heterogeneity in already reported relative risks at different cancer sites indicates that there is probably not a universal mechanism by which obesity drives cancer development. For example, the attributable fraction of endometrial cancers is approximately 41 % *v.* 10 % for cancers of the colon⁽¹²⁾. The main caveat concerning the association between obesity and cancer is the fact that a number of other environmental factors including dietary composition, energy intake and physical activity represent important confounding factors in obese patients, and no specifically designed prospective studies have yet to demarcate the relative contribution of each.

Pathological inflammation in obesity is associated with insulin resistance and altered cellular energetics

Obesity-associated inflammation and cancer are inextricably linked and despite robust epidemiological evidence connecting obesity and cancer, the pathophysiological mechanisms underpinning the association remain poorly characterised^(17,18). The expanded adipose tissue mass associated with an obese phenotype is deposited in both the intra-abdominal compartment, where it is known as central or visceral adiposity, and beneath the skin, where it is called subcutaneous adipose tissue. Visceral adipose tissue (VAT) is more highly correlated with an altered glucose and lipid metabolic profile as well as increased risk of CVD than subcutaneous adipose tissue^(19–21). Obese patients often have a relative abundance of fat in one or other compartment⁽²²⁾. Those with excess visceral fat have an increased risk (independent of BMI) of breast cancer, oesophageal adenocarcinoma, colorectal adenocarcinoma and colorectal adenoma^(9,23–26).

Adipose tissue in obese subjects has altered endocrine function and a secretory profile with predominantly pro-inflammatory cytokines, which are secreted by both adipocytes (and called adipokines) and immune cells. This results in a state of chronic low-grade inflammation which is thought to be pro-tumourigenic^(27–29). Inflammation provides the selective pressure that may fuel the accumulation of mutations driving tumour growth and survival and could result in poor immune surveillance of tumours once they develop⁽³⁰⁾. The relative contribution of each individual adipokine to this systemic inflammation is not understood and it is likely that a complex interplay between the various pro- and anti-inflammatory immune cells and their secreted cytokines contributes to tumourigenesis.

Another consequence of systemic inflammation in the obese state is insulin resistance and T2DM⁽³¹⁾. These conditions are associated with increased levels of inflammatory mediators including acute phase reactants such as fibrinogen, C-reactive protein, IL-6, plasminogen activator inhibitor-1^(32–34). The prevalence of insulin resistance increases as body weight increases and can be

reversed with weight loss^(35,36). Epidemiological studies on the role of T2DM in carcinogenesis report consistent increases in cancer incidence at certain sites, which display considerable overlap with those sites associated with obesity-associated cancers as previously described, including liver in particular, as well as pancreas, endometrium, breast, colorectal, bladder, non-Hodgkin's lymphoma and kidney cancers⁽³⁷⁾.

Diet-induced insulin resistance develops as a metabolic adaptation to increased circulating levels of non-esterified fatty acids (NEFA), which are constantly released from adipose tissue, especially from visceral fat stores⁽¹⁴⁾. Increased NEFA levels force liver, muscle and other tissues to shift towards increased storage and oxidation of fats for their energy production⁽³⁸⁾. The compensatory effect is a reduced capacity of these tissues to absorb, store and metabolise glucose. Patients with insulin resistance also exhibit a reduction in cellular insulin-receptor levels and reduced responsiveness of some intracellular transduction pathways mediating the effects of insulin binding to its receptor⁽³⁹⁾. Interestingly, insulin resistance leads to increased insulin production and the mitogenic effects of insulin have been associated with several cancers^(24,40,41). The insulin-like growth factor (IGF) axis comprising two growth factors (IGF-1 and IGF-2) as well as a number of binding proteins and two receptors (IGF-1R and IGF-2R), sharing homology with the insulin receptor, has been cited as a mediator of hyperinsulinaemia on cell growth and energy metabolism⁽⁴²⁾. Increased expression of IGF-1R is reported in a number of cancer subtypes but a large systematic review and meta-analysis of studies of serum concentrations of IGF-1 and insulin as biomarkers reveals there to be significant bias found in the studies which have been published in the literature^(43–46). New prospective specifically-designed epidemiological studies are warranted to help clarify the relative contribution of insulin resistance, inflammation and obesity to cancer development.

Changes in cellular energetics and dysregulated metabolism are hallmarks of cancer and it is not surprising that associations between metabolic changes and obesity are being uncovered⁽⁴⁷⁾. Recent findings of our group show that secreted factors from VAT of obesity-associated cancer patients induce metabolic changes in oesophageal adenocarcinoma cell lines; increasing mitochondrial mass, mitochondrial membrane potential and inducing a shift to glycolysis⁽⁴⁸⁾. Moreover, these studies identified a positive correlation between obesity and the expression of the glycolytic marker pyruvate kinase M2 in the tumours of oesophageal adenocarcinoma patients supporting a shift to glycolysis in obesity. Further analysis revealed that the VAT of obese oesophageal adenocarcinoma patients exhibited a glycolytic profile with increased expression of lactate, an established carcinogen^(48,49). Therefore, these data present a possible link between obesity and the dysregulated bioenergetics that are characteristic of cancer, thus providing a mechanism through which increased VAT mass might promote tumourigenesis.

The sex differential in cancer incidence in obese patients has also been repeatedly reproduced in epidemiological studies^(8,12). This, as well as the marked

increased incidence in endometrial cancers in obese females in particular, has led to the hypothesis that sex hormones play a role in the carcinogenic process in obesity, at least for some sites. There is a well-recognised association between the development of endometrial cancer and oestrogen excess^(50,51). A factor analysis of inflammatory, insulin-regulated physiological axes and sex steroids measured from the pre-diagnostic serum levels of patients enrolled in the European Prospective Investigation into Cancer and Nutrition cohort compared patients who developed endometrial cancer *v.* matched controls⁽⁵²⁾. This allowed an analysis of these highly correlated biomarkers for their relative contribution to endometrial cancer development and demonstrated a contribution to cancer risk in all three of these axes.

In light of the metabolic changes that occur with increasing visceral adipose tissue mass, it stands to reason that obesity may be a confounding factor when developing immune-based anti-cancer therapies for obesity-associated malignancies. However, an improved understanding of the interplay between the immunity–obesity–cancer axis may allow novel insights into cancer development, and can allow improvement of current strategies for personalised therapy.

Adipokines and immune function

In addition to their direct roles in cellular energetics and metabolism⁽⁵³⁾, emerging evidence demonstrates roles for adipokines in immune system regulation. For example, leptin, produced by adipose tissue, is a long-term regulator of weight and acts via its receptor to decrease appetite and food intake and increase energy consumption⁽⁵⁴⁾. Leptin is also a pro-inflammatory cytokine inducing activation of T cells and Th1 cell differentiation⁽⁵⁵⁾. It also modulates the function of all other immune cell lineages (but only in the presence of other non-specific immunostimulants)⁽⁵⁶⁾. Leptin is induced by inflammatory cytokines such as IL-1, IL-6 and lipopolysaccharide⁽⁵⁷⁾. It could be hypothesised that the relative lack of some subpopulations of T cells (CD3⁺, CD4⁺CD45RO⁺, CD8⁺)⁽⁵⁸⁾ could be related to the leptin resistant state prevalent in obese subjects⁽⁵⁹⁾. Adiponectin is an abundant adipokine secreted by adipocytes in VAT. Circulating levels are inversely associated with obesity⁽⁶⁰⁾ and decreased expression of adiponectin is closely correlated with insulin resistance^(61,62). Adiponectin inhibits macrophage phagocytosis and reduces macrophage production of pro-inflammatory IL-6 and TNF- α and increases production of anti-inflammatory IL-10 and IL-1R⁽⁶³⁾.

Innate and adaptive immunity in obesity and cancer

Obesity induces a state of pathological chronic inflammation, marked by elevated levels of NEFA, abnormal cytokine production and activation of inflammatory signalling pathways^(64–68). The expanded vasculature and increased blood supply that accompanies the expansion of VAT in obesity, results in increased inflammatory

Table 2. Summary of immunological impact of obesity in human and potential therapeutic targets

Cell type	Subset	Normal function	Function in obesity	Immunotherapeutic potential – reference
Macrophage	M1	Pro-inflammatory	Accumulate in VAT, drive adipose tissue inflammation ⁽³¹⁾ , important in insulin resistance ⁽⁷¹⁾	(72)
	M2	Anti-inflammatory, immunoregulatory, tissue surveillance and remodelling functions, control insulin sensitivity	Diminished in VAT (M1 predominance)	
CD4 ⁺ T	T _{H1}	Pro-inflammatory; anti-bacterial, anti-viral, anti-tumour	Promote inflammation ^(65,73) , macrophage recruitment	(74,75)
	T _{H2}	Anti-parasitic function; antibody production, eosinophil activation	Decreased in VAT ⁽⁷⁶⁾	
	T _{H17}	Pro-inflammatory (neutrophils)	Enriched in adipose tissue ⁽⁷⁷⁾	(78)
	T _{reg}	Immunoregulation	Decreased in omentum, undifferentiated phenotype ⁽⁷⁶⁾	(79)
CD8 ⁺ T		Cytotoxicity – directly kill abnormal cells	Promote inflammation ⁽⁸⁰⁾ , macrophage recruitment	(81,82)
NK		Cytotoxicity – kill abnormal cells	Decreased in blood, impaired function ⁽⁸³⁾	(84)
iNKT		Cytotoxicity – kill abnormal cells	Immunoregulatory role ⁽⁸³⁾	(85)
γδ T cells	Vδ1	Cytotoxicity – kill abnormal cells		(86)
	Vδ2	Cytotoxicity – kill abnormal cells, T _{H1} -like pro-inflammatory	Decreased in blood, impaired function ⁽⁸⁷⁾	(88)
	Vδ3	Cytotoxicity – kill abnormal cells, T _{H1} and T _{H17} cytokine profile		
MAIT		Pro-inflammatory, kill bacteria-infected cells, IL-17 production	Decreased and dysregulated function (IL-17) ^(89,90)	

iNKT, invariant natural killer T cells; MAIT, mucosal associated invariant T cells; NK, natural killer; VAT, visceral adipose tissue.

immune cell infiltration, enhanced pro-inflammatory cytokine release and ultimately local and systemic tumourigenic inflammation^(69,70). The alterations in immune cell repertoires in the peripheral blood, VAT and proximal tissues, in particular liver, continue to be investigated in an effort to elucidate the extent of immune dysregulation in obesity. Immunotherapeutic strategies to reset the balance between pro- and anti-inflammatory cells could also be crucial to restoring immune control, attenuating obesity-associated inflammation and treating/preventing resultant disease. However the immune dysregulation in obesity with underlying malignancy could significantly negatively impact on anti-tumour immunity. In fact, ideal immunotherapeutic approaches in obesity-associated cancer should attenuate chronic systemic inflammation while simultaneously augmenting specific immunity at the tumour site. Research is required to fully characterise the immune cell repertoires in the periphery, VAT and tumour of obesity-associated cancer patients to distinguish between the subsets that drive tumourigenic inflammation, those that control it and those that are crucial for tumour eradication. For the purpose of this review, we will focus on the present knowledge of conventional T lymphocytes, innate lymphocytes and macrophages in obesity and cancer (Table 2).

Conventional T cells

CD4⁺ and CD8⁺ T cells comprise the antigen-specific effector arm of the adaptive immune response and elicit

their effector functions through cytokine production and cytotoxic activity. In the CD4⁺ T cell compartment, Th1 cells produce interferon (IFN)-γ, TNF-α and IL-2, while T helper type 2 (Th2) cells express IL-4, IL-5 and IL-13^(91,92). Inflammatory T helper type 17 (Th17) cells express IL-17 and IL-22 and regulatory T (T_{reg}) cells express IL-10 and transforming growth factor β^(93,94). CD8⁺ T cells are the key cytotoxic T lymphocytes but are also potent cytokine producers. Therefore in the context of malignancy, tumour infiltration of the appropriate CD4⁺ and CD8⁺ T cell milieu is crucial for tumour eradication⁽⁹⁵⁾. In fact, the ratio of cytotoxic T lymphocytes to T_{reg} cells can be predictive of outcome^(96,97). In obesity, our group and others have reported enrichments of activated and effector pro-inflammatory CD4⁺ and CD8⁺ T cells in VAT and have identified these cells as key players in inflammatory macrophage recruitment and inflammatory cytokine production, thus contributing to the initiation and maintenance of obesity-associated inflammation^(65,73,80). Furthermore, we have previously reported significantly higher frequencies of such IFN-γ-producing T cells in the VAT of obesity-associated cancer patients, compared with non-cancer control subjects⁽⁶⁵⁾. In recent unpublished studies, we have also observed enrichments of TNF-α and IL-17-producing T cells in the VAT, demonstrating that more than one inflammatory T cell subset is contributing to adipose tissue inflammation in obesity and obesity-associated cancer. In contrast, while T_{reg} cells are enriched in lean VAT, their frequency is significantly diminished in obese VAT⁽⁹⁸⁾. Therefore,

VAT in obesity is rich in pro-inflammatory cytokine-producing effector T cells and a relative deficiency of T_{reg} cells^(66,80,98). Such approaches to reset the balance between regulatory and inflammatory T cell subsets may potentially attenuate pathological inflammation in obesity.

Natural killer cells

Natural killer (NK) cells are MHC-unrestricted lymphocytes and comprise a major component of innate lymphocytes in human blood and liver, comprising 10–15 and 30 % of total lymphocytes, respectively⁽⁹⁹⁾. NK cells display powerful cytotoxic activities once activated, and are potent producers of pro-inflammatory cytokines including IFN- γ and TNF- α which can contribute to the modulation of adaptive immune responses and direct anti-tumour effects^(99–101). In the context of inflammatory disease, NK cells have been implicated in the pathogenesis of inflammatory bowel disease and psoriasis^(102,103). However as of yet, their role has not been fully elucidated in the chronic inflammation that is characteristic of obesity. Lynch *et al.* have reported significant reductions of circulating NK cells in metabolically unhealthy obese subjects, suggesting that a lack of NK cells in the periphery is detrimental for metabolic health⁽⁸³⁾. Lynch *et al.* also reported significant expansions of circulating inhibitory-receptor bearing and CD69⁺ NK cells in metabolically unhealthy obese individuals, compared with healthy controls, suggesting that peripheral NK cells in metabolically unhealthy obese patients were activated but unable to elicit effector functions, making such individuals more susceptible to disease⁽⁸³⁾. Furthermore, circulating NK cells from obese subjects were found to be less effective at killing tumour cells than their counterparts in lean subjects, suggesting that obese individuals have impaired defences against malignancy⁽¹⁰⁴⁾. More recently, a study by O' Rourke *et al.* revealed expansions of the CD56^{BRIGHT} (main cytokine producing subset) of NK cells in obese VAT, indicating that cytokine-producing fractions of NK cells are more prevalent in obesity⁽¹⁰⁵⁾. Moreover, NK cells were identified as key players in macrophage recruitment to adipose tissue but did not affect overall secreted inflammatory cytokine levels⁽¹⁰⁶⁾. In fact, the macrophage population recruited to the VAT by NK cells in this study was not the macrophage subset implicated in VAT inflammation and therefore, the role of NK cells in adipose tissue inflammation was unclear. However, new data gathered by Wensveen *et al.* demonstrates that IFN- γ -producing NK cells are pivotal in M1 macrophage polarisation in the adipose tissue of obese mice and subsequent insulin resistance, but similar results have yet to be reported in human subjects⁽¹⁰⁷⁾. Interestingly, this study was the first to report a direct interaction between NK cells and adipocytes through the mouse equivalent of NK receptor P46 (NKP46) natural cytotoxicity receptor 1 (NCR1), and shows that NK cells and adipocytes together drive inflammatory macrophage recruitment and contributes to adipose tissue inflammation in mice. With respect to therapeutic

avenues, NKP46 might be a potential target to attenuate NK cell and adipocyte-mediated inflammation. Since mouse and human NK cells are characterised differently, it is first important to fully investigate the NK repertoires in human blood and VAT, elucidate their interactions with adipocytes, their cytokine profiles and subsequent contribution to inflammatory cell recruitment and adipose tissue inflammation. Furthermore, the investigation of the NK cell milieu in blood, VAT and tumour of patients with obesity-associated malignancy is warranted to completely understand the changes that NK cells undergo in human obesity and how this impacts anti-tumour immunity and patient outcomes.

Invariant natural killer T cells

Invariant NKT (iNKT) cells are a subset of MHC-unrestricted innate lymphocytes that respond rapidly, elicit potent IFN- γ production and cytotoxic activity and modulate adaptive immune responses, thus making them key players in anti-tumour immunity. They express a restricted T cell receptor repertoire consisting of a Va14Ja18 α -chain in mice and a Va24Ja18 α -chain in human subjects, paired with a limited number of β -chains⁽¹⁰⁸⁾. Such cells also express a number of cell-surface markers typically expressed on NK cells, hence the name NKT cell, and recognise lipid antigen presented by the MHC-like glycoprotein, CD1d^(108–111). The most potent activator of iNKT cells isolated to date is the marine sponge-derived glycolipid α -galactosylceramide (α -GalCer), which has been shown to induce anti-tumour cytotoxic activity and cytokine production in mice leading to the inhibition of tumour growth⁽¹¹²⁾. However, α -GalCer has proven much less effective in human subjects due to the lower abundance of iNKT cells in human subjects compared with mice⁽¹¹³⁾. VAT is the only human tissue reported to have a high proportion of iNKT cells, averaging 10 % in healthy subjects⁽⁸³⁾. However, in the setting of obesity the frequencies of iNKT cells are diminished and this depletion is reversed following weight loss⁽¹¹⁴⁾. VAT iNKT cells preferentially secrete higher levels of IL-10, compared with the Th1 cytokine profile they exhibit in other tissues, suggesting that iNKT cells in adipose tissue predominantly serve an immune regulatory role⁽¹¹⁴⁾. Furthermore, the adoptive transfer of iNKT cells into obese mice can induce weight loss and improve insulin sensitivity, implying that iNKT cells are pivotal for metabolic health and protective against insulin resistance. This may suggest that metabolically unhealthy individuals might benefit from iNKT cell-based therapies and that IL-10-producing VAT iNKT cells may prove useful in the attenuation of obesity-associated inflammation. However, iNKT cell therapeutic potential in obesity-associated cancer has yet to be uncovered.

Gamma/delta T cells

Human $\gamma\delta$ T cells are another type of innate or unconventional T cell subset, typically comprising 1–5 % of

circulating adult T cells, and are also found within the gut⁽¹¹⁵⁾, skin⁽¹¹⁶⁾, lung⁽¹¹⁷⁾ and uterus⁽¹¹⁸⁾. In human subjects there are three main $\gamma\delta$ T cell types, defined by their T cell receptor delta chain (called V δ 1, V δ 2 or V δ 3, respectively), which can be paired with various gamma chains⁽¹¹⁹⁾. $\gamma\delta$ T cells respond rapidly to infection or stress signals and display anti-viral, anti-bacterial, anti-parasitic and anti-tumour functions, and a strong Th1 predominance⁽¹²⁰⁾. The main subset of circulating human $\gamma\delta$ T cells (V γ 9V δ 2 T cells) recognises pyrophosphate antigens derived from bacterial or endogenous sources. The precise antigens recognised and modes of antigen recognition for other $\gamma\delta$ T cell subsets are presently unclear but it is known that MHC-mediated antigen presentation is not required^(121,122). In mouse models, $\gamma\delta$ T cells produce copious amounts of IL-17⁽¹²³⁾, and comprise the predominant T cell subset found in tissues⁽¹²⁴⁾, whereas this is not the case in human subjects. Furthermore, the predominant $\gamma\delta$ T cell subset in human blood, the V γ 9V δ 2 T cell subset, is only found in human subjects and other higher primates. All three $\gamma\delta$ T cell subsets in the human demonstrate potent and specific anti-tumour cytotoxicity against a range of different tumour types^(119,125,126) and as a result, their use as immunotherapeutic agents is presently under investigation⁽⁸⁸⁾. Meta-analysis of clinical trial data shows limited success with present immunotherapeutic approaches used to date however, most of which involve adoptive transfer of V γ 9V δ 2 T cells. It is hoped that an improved understanding of $\gamma\delta$ T cell biology and subset differences will improve future immunotherapeutic strategies.

In obese individuals, there is an inverse correlation between the frequency of circulating $\gamma\delta$ T cells and increasing BMI⁽⁸⁷⁾, with obese individuals having, on average, more than four times fewer circulating V γ 9V δ 2 T cells than non-obese donors. Remaining $\gamma\delta$ T cells have a skewed maturation phenotype similar to that observed in aged populations, a blunted IFN- γ response and reduced IL-2 receptor α chain expression. Constanzo and colleagues reported that this dysregulation could be overcome by stimulation of cells with pyrophosphate antigens and addition of IL-2⁽⁸⁷⁾. IL-2 acts as a growth factor for $\gamma\delta$ T cells, suggesting that cellular dysfunction in obesity may be via growth factor deprivation rather than cell incapacitation. In mouse models of obesity, $\gamma\delta$ T cells are shown to promote insulin resistance and inflammation via recruitment of macrophages to adipose tissue⁽¹²⁷⁾, though whether this also applies in human subjects remains to be investigated. The role of $\gamma\delta$ T cells in the underlying inflammation and anti-tumour responses in the setting of obesity-associated cancer has yet to be elucidated. Our group are currently investigating the distribution and functional phenotype of $\gamma\delta$ T cell subsets in the periphery, VAT and tumour of obesity-associated cancer patients in order to identify their usefulness in the prophylaxis and treatment of such malignancies.

Mucosal associated invariant T cells

Mucosal associated invariant T (MAIT) cells are a population of invariant T cells comprising 1–5 % of T cells in

human blood, and are defined by expression of an invariant V α 7-2-J α 33 chain and high levels of the NK cell marker CD161⁽¹²⁸⁾. MAIT cells are enriched in human adipose tissue and in mucosal and inflamed tissues, where they recognise vitamin B₂ metabolites produced by bacteria and yeasts⁽¹²⁹⁾. MAIT cells thus recognise and kill bacteria-infected cells⁽¹³⁰⁾. While MAIT cells have been described in breast cancer and are reportedly resistant to chemotherapy treatment⁽¹²⁹⁾, their role in cancer is as yet unknown. MAIT cell frequency is dramatically decreased in the blood and adipose tissues of patients with T2DM and/or severe obesity compared with control donors, and this depletion is associated with diabetic status^(89,90). Moreover, in both patient groups, circulating MAIT cells display an activated phenotype that is associated with elevated Th1 and Th17 cytokine production. In obese patients, MAIT cells are more abundant in adipose tissue than in blood and exhibit a striking IL-17 profile, a cytokine implicated in insulin resistance. Similar results were also observed in an obese paediatric cohort⁽⁸⁹⁾. MAIT cell frequencies increase while their cytokine production decreases in obese patients after bariatric surgery, in line with improvements in metabolic parameters. These studies reveal profound abnormalities in MAIT cells in patients harbouring metabolic disorders, suggesting their potential role in these pathologies, yet future work remains to determine the role for MAIT cells in obesity-associated cancers.

Macrophages

While macrophages play a crucial role in innate immunity, their polarisation to an M1 phenotype positions them as key drivers of pathological inflammation, while a dominant M2 phenotype can facilitate their immune suppressive role in the tumour microenvironment^(131,132). M1, or classically-activated macrophages, are regarded as the more inflammatory subset, while M2 macrophages are considered anti-inflammatory and immunoregulatory. Macrophages recruited to the tumour microenvironment can maintain an M1 phenotype and elicit potent IFN- γ , TNF- α , IL-12 and chemokine production, promote T cell activation and mediate anti-tumour activity⁽¹³³⁾. However, upon recruitment to the tumour microenvironment, macrophages are often polarised toward an M2 phenotype and become tumour-associated macrophages which produce immunomodulatory and pro-angiogenic factors including IL-10, TGF- β , vascular endothelial growth factor and matrix metalloproteinase 9⁽¹³³⁾. In the obese setting, several studies have implicated M1 macrophages as drivers of adipose tissue inflammation, with T cells and NK cells contributing to their recruitment and polarisation^(31,80,107,134). In fact, M1 macrophages are believed to be the main producers of IL-1 β and TNF in obesity and key players in insulin resistance⁽¹³⁵⁾. Furthermore, while the chemokine system plays a central role in macrophage recruitment to adipose tissue and the development of insulin resistance, the inhibition of one chemokine alone is not enough to block macrophage accumulation in murine models of

obesity^(136,137). Therefore, future studies might investigate the inhibition of more than one chemokine pathway to block M1 macrophage accumulation in obese VAT and alleviate chronic inflammation. Blocking chemokine-guided recruitment of macrophages to tumour might attenuate tumour-associated macrophage-mediated immune suppression and angiogenesis in cancer and prove useful in cancer immunotherapy. However, it is now understood that tumour-associated macrophage phenotype and function is critically influenced by the tumour microenvironment and therefore exploiting such environmental cues might be a preferable therapeutic approach⁽¹³⁸⁾.

Immunometabolism in obesity and cancer

In recent years, research has revealed how immune cell metabolism supports and controls immune function, and has led to a focus on exploiting immunometabolism to treat inflammation and cancer. In brief, more activated and rapidly dividing immune cells rely on glycolysis to maintain their biomass and energy levels, while more quiescent and regulatory immune cells mainly utilise oxidative phosphorylation (OxPhos)⁽¹³⁹⁾. Depending on the stage of their development, T cell subsets possess strikingly different metabolic profiles which reflect their energetic and biosynthetic requirements, which in turn support their function^(140,141). Naive T cells are usually metabolically quiescent and use OxPhos as the main means of generating ATP, while rapidly proliferating effector CD4⁺ Th1, Th2 and Th17 cells and CD8⁺ cytotoxic T cells utilise significantly elevated levels of glycolysis to meet their energy requirements^(140–146). Following resolution of the immune response, the remaining pool of memory T cells mainly utilise OxPhos and lipid oxidation to meet their lower turnover rates and to support their longevity, as do T_{reg} cells^(147,148). Manipulation of such cellular metabolic pathways might represent a novel means of therapeutically skewing immune responses. Since our group and others have shown that pro-inflammatory Th1 cells are key players in obesity-associated inflammation while T_{reg} cells are depleted, a targeted therapy to alter T cell metabolic profile and attenuate T cell-mediated inflammation in the VAT may present favourable outcomes in obesity and obesity-associated cancer^(66,80,149,150). Similarly, inflammatory M1 macrophages, other key players in adipose tissue inflammation, and antibody-secreting B cells also rely on glycolytic processes to fuel their inflammatory functions while M2 macrophages use fatty acids to support OxPhos^(134,151,152).

Exploitation of immune cell metabolism might be utilised as a prophylactic to prevent obesity-associated disease or to treat obesity-associated cancer. For instance, inhibition of both the mammalian target of rapamycin and mitogen-activated protein kinase (extracellular signal-regulated kinase) pathways using rapamycin and the mitogen-activated protein kinase inhibitor PD325901 robustly blocked effector CD4⁺ T cell proliferation and decreased disease severity in a mouse

model of arthritis⁽¹⁵³⁾. Since our group have found pro-inflammatory effector T cells to be enriched in the inflamed omentum in obesity, extracellular signal-regulated kinase and mammalian target of rapamycin inhibitors might elicit a similar anti-inflammatory effect in obesity⁽⁶⁶⁾. Others have found that beauvericin-mediated inhibition of T cell activation and pro-inflammatory cytokine production in an animal model of colitis was achieved by targeting P13 K and AKT and resulted in reduced weight loss, diarrhoea and mortality⁽¹⁵⁴⁾. More recently, inhibition of AKT in expanded tumour-infiltrating lymphocytes resulted in increased rates of OxPhos and fatty acid oxidation⁽¹⁵⁵⁾. This led to enhanced *in vivo* persistence of such memory T cells and augmented anti-tumour immunity following adoptive transfer⁽¹⁵⁶⁾. Therefore, AKT inhibition might serve to dampen pro-inflammatory effector T cells in the VAT and simultaneously promote tumour-specific memory T cell responses at the tumour site, thus possibly offering a novel immuno-metabolomic therapeutic approach for chronically inflamed obesity-associated cancer patients. However, there is first an urgent need to perform focussed studies to elucidate the metabolic profiles of pro- and anti-inflammatory immune cells in the VAT and tumour of such patients.

Future prospects for obesity-associated cancer: prevention v. treatment

It is estimated that one in every four cancer cases is preventable by implementing lifestyle changes. Furthermore, studies such as the Women's Intervention Nutrition Study have shown that reduction of fat in the diet of women with breast cancer and associated weight loss reduced the relative risk of cancer recurrence by 24 %⁽¹⁵⁷⁾. Prevention and management of obesity is therefore a major therapeutic goal. Intervention before the pathological inflammatory cascade ensues and immune system becomes excessively dysregulated is the ideal prophylactic approach. However, there have already been multiple government campaigns, legislation amendments and educational reforms to promote healthier lifestyle but with escalating obesity rates, a more aggressive approach is certainly needed. Griggs & Sabel argue for the benefits of aggressive promotion of lifestyle changes by physicians as part of the cancer patient treatment plan⁽¹⁵⁸⁾. However, obesity is a complex variable, and BMI is not always a reliable measure of metabolic health. Schmitz *et al.* suggest that further clarification of the biological-social-environmental feedback loop is required in order to elucidate the combined and independent contributions of race, ethnicity, comorbidities and obesity on cancer survival and adverse treatment effects⁽¹⁵⁹⁾.

This review highlights the critical importance of understanding the obesity–immunity–cancer axis and the fact that obesity driven immunological dysregulation should no longer be ignored when developing immunotherapeutic strategies. Immunotherapies such as pembrolizumab (Merck), nivolumab and ipilimumab

(Bristol Meyer Squibb) have recently gained Food and Drug Administration approval and are so far, proving effective for a number of different cancers (www.clinicaltrials.gov). However, their suitability has not been thoroughly scrutinised under the pre-existing inflammatory condition of obesity. The challenge of using checkpoint inhibitors in obesity-associated cancer is to alleviate immune suppression and augment anti-tumour responses without inducing excessive pro-tumourigenic inflammatory cytokine production by T cells, which have already been shown to drive adipose tissue inflammation in obesity^(65,80). In the context of chronic obesity-associated inflammation, there is cause for concern with such immunotherapies, since blocking programmed death-ligand 1 has previously been shown to enhance monocyte function by decreasing IL-10 and enhancing inflammatory cytokine production⁽¹⁶⁰⁾. Furthermore, aged obese mice were observed to have the most extreme pathological responses to anti-CD40 and IL-2 therapy, causing cytokine storms, organ pathology and eventual death⁽¹⁶¹⁾. Therefore, the use of such elegant immunotherapeutic approaches might be theoretically desirable for obesity-associated malignancy but first, their potential to exacerbate inflammation in obesity must be fully investigated. In the context of obesity-associated cancer, targeting the correct tissue rather than a systemic immunotherapeutic approach is also of paramount importance, when aiming to enhance anti-tumour immunity without contributing to adipose tissue and systemic inflammation. For instance, augmenting anti-tumour immunity without exacerbating inflammation might be achieved through the adoptive transfer of T or NK cells, already primed with a chemotactic signal toward the tumour site and not the adipose tissue, as demonstrated by Wennerberg *et al.*⁽¹⁶²⁾. Similarly, approaches might combine adoptive transfer with chemokine treatments to enhance anti-inflammatory cell migration to the VAT and attenuate pathological inflammation. For instance, M2 macrophages, T_{reg} cell and iNKT cell numbers might be replenished in the obese VAT to restore immune balance and prevent progression to inflammation-driven disease. Already, adoptive transfer of iNKT cells has been shown to reduce weight loss and improve insulin sensitivity⁽¹¹⁴⁾. Furthermore, the Th2 proportion of CD4⁺ T cells adoptively transferred into mouse models of obesity has also been shown to reverse weight gain and insulin resistance⁽¹⁶³⁾. However the specific chemokine pathways guiding the key T, NK and iNKT cells to the tumour and to inflamed tissue sites must first be elucidated before such combination immunotherapies can be considered.

It is now evident that several critical factors must be taken into consideration when developing successful immunotherapeutic approaches. Firstly, evaluation of the immunological environment must be considered. Overwhelming data shows a dearth of innate lymphocytes or their inactivation and general dysregulation in obesity (e.g. $\gamma\delta$ T cells and MAIT cells are reduced with increasing BMI)^(87,89,90). It may be useful to evaluate the level of immune involvement in the tumour microenvironment, and evaluate the degree of immune

cell dysregulation prior to devising a patient treatment plan. Indeed, evaluation of immunological parameters is presently in development as a prognostic aid, and shows superior predictive ability compared with traditional histopathological staging methods in colorectal cancer^(164–166). Galon *et al.* show that evaluation of the type, density and location of immune cell infiltration into tumours can allow prediction of patient survival⁽¹⁶⁵⁾. A greater understanding of the underlying biology behind immunotherapy is also urgently required. Checkpoint inhibitors such as ipilimumab and tremelimumab have been hailed as breakthrough drugs, but show no benefit in the majority of patients and there is a paucity of published data in the obesity-associated cancer space⁽¹⁶⁷⁾. Recent work shows there may be a genetic basis for clinical responses in a cohort of melanoma patients⁽¹⁶⁷⁾. Improved understanding of the immunological landscape in obesity and cancer will undoubtedly allow development of further breakthroughs, for example combination immunotherapy approaches may be advantageous, combining selective cytokine or chemokine replenishment or depletion strategies with checkpoint inhibitors, adoptive transfer and traditional chemoradiotherapy strategies or hormone therapies for maximum effect. Some success has already been reported when anti-PD-1 (programmed cell death protein 1) and anti-CTLA4 (cytotoxic T lymphocytes antigen-4) therapies are administered together⁽¹⁶⁸⁾. Replenishment of growth factors that are lacking in obesity may be a useful addition to existing immunotherapeutic strategies, such as reconstituting IL-2 levels in order to boost $\gamma\delta$ T cell responses. Simultaneous neutralisation of certain pro-inflammatory cytokines (e.g. IL-17, IL-1, IL-6) may also be warranted in obese patients to fully overcome immunological dysregulation. Optimal dosing and timing strategies will also require further consideration, particularly in regard to treating patients with elevated BMI⁽¹⁶⁹⁾.

In conclusion, global health is now plagued by pathologies that have arisen from an obesity epidemic that shows little sign of abating. This review has focused on the potential role of a dysregulated immune system in a growing number of obesity-associated cancers. With a new generation of immunotherapies which includes the checkpoint inhibitors nivolumab and ipilimumab anticipated to change the face of cancer treatment and improve survival for a number of cancer types, it is important that the chronic inflammation underpinning obesity-associated cancer is better understood. Over the past 10 years, there has been an increase in studies in human subjects investigating the phenotypes and functions of immune cells in adipose tissue, together with their role in obesity-associated disease, including cancer, however at this time there is scant understanding of how this knowledge can be used to therapeutic advantage with targeted approaches. Accordingly, further research investigating the immune compartments and chemokine and cytokine networks underpinning inflammation-driven obesity-related malignancy in human subjects is of immediate relevance and importance. Also, in the wake of multiple campaigns which have failed to halt growing obesity

Prophylaxis of obesity-associated pathologies

Multiple interventions to aggressively combat obesity: parental education, portion control, healthy food accessibility, workplace initiatives, active transport, media restrictions, and labelling, surgery, pharmaceuticals, etc.

+/-

Adoptive transfer of anti-inflammatory iNKT or T_{reg} cells + chemokine therapy to direct chemotaxis to adipose tissue to alleviate inflammation.

Targeted Glut1 blocking to alter energy metabolism and shift to glycolysis

Inhibition of mTOR and MAPK (ERK) pathways to ↓ effector CD4⁺ T cell proliferation and ↓ inflammation

Treatment of obesity-associated cancer

Standard therapy (Chemoradiotherapy, resection)

+/-

Akt inhibition to promote memory T cell persistence and suppress inflammation

Adoptive transfer + chemokine therapy to direct anti-inflammatory cells to VAT and/or cytotoxic cells to tumour

Full investigation of checkpoint inhibitor safety in inflamed setting of obesity-associated cancer.

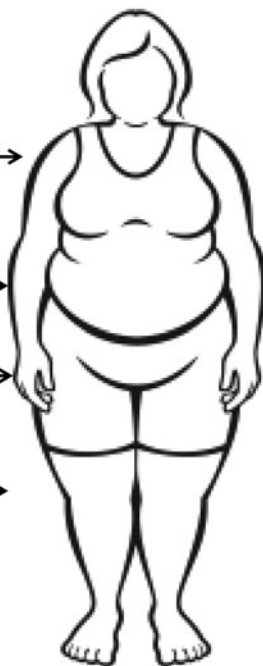


Fig. 1. Future approaches for the prevention and treatment of obesity-associated cancer (10,11,139). iNKT, invariant natural killer T cells; T_{reg}, regulatory T cells; mTOR, mammalian target of rapamycin; MAPK (ERK), mitogen-activated protein kinase (extracellular signal-regulated kinase); VAT, visceral adipose tissue.

rates, more hard-line approaches are urgently required to promote lifestyle change and nutritional education. Childhood obesity must be tackled to prevent a further upsurge in obesity-associated cancer incidence among future generations. In addition to laboratory-based research, a joint effort between clinicians, research scientists, dietitians and governing bodies is needed to focus on the preventability of obesity through diet and lifestyle. Exploring these avenues will allow a multi-pronged approach to combating this burgeoning health crisis.

Conclusion

While there is a plethora of research implicating a dysregulated immune system in obesity-associated inflammation and related pathologies, further work is urgently required to identify novel approaches to prevent and treat obesity-associated diseases such as cancer. Evidence suggests that a combination of both immunotherapy- and lifestyle-based approaches may reduce incidence and improve outcomes for obesity-associated malignancy.

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Conflict of interest

None.

Authorship

J. V. R. presented the work and was responsible for the concept, direction and supervision of the manuscript. C. L. D. and M. R. D. researched and prepared sections for the manuscript. M. J. C. researched and prepared sections for the manuscript and was responsible for manuscript assembly.

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