Abstract

A subacute inflammatory phenotype is implicated in the pathology of insulin resistance (IR) and type 2 diabetes mellitus. Interleukin (IL)-1α and IL-1β are produced by innate immune cells, including macrophages, and mediate their inflammatory response through the IL-1 type I receptor (IL-1RI). This study sought to understand the transcriptomic signature of adipose tissue in obese IL-1RI−/− mice. Following dietary intervention, markers of insulin sensitivity and inflammation in adipose tissue were determined, and gene expression was assessed with microarrays. IL-1RI−/− mice fed a high-fat diet (HFD) had significantly lower plasma inflammatory cytokine concentrations than wild-type mice. Metabolic network analysis of transcriptomic effects identified up-regulation and co-expression of genes involved in lipolysis, lipogenesis and tricarboxylic acid (TCA) cycle. Further assessment of gene expression in a network of protein interactions related to innate immunity highlighted Stat3 as a potential transcriptional regulator of IL-1 signalling. The complex, downstream effects of IL-1 signalling through the IL-1RI receptor remain poorly defined. Using network-based analyses of transcriptomic signatures in IL-1RI−/− mice, we have identified expression changes in genes involved in lipolysis and the TCA cycle, which may be more broadly indicative of a restoration of mitochondrial function in the context of HFD. Our results also highlight a potential role for Stat3 in linking IL-1 signalling to adipogenesis and IR.

Keywords: Inflammation; IL-1 receptor type I; Transcriptomic profiling; Network analysis; Insulin resistance; Adipose tissue
analysis [22]. However, from a systems biological perspective, global network-based approaches carry the advantage of highlighting inherent interaction and overlapping of functionally related pathways.

Despite growing evidence for a functional role of IL-1 in adipose tissue function, the complex downstream consequences of IL-1 signaling remain poorly clarified — particularly with respect to diet-induced obesity and adipose tissue remodelling. We therefore used a network-based approach to analyze adipose tissue gene expression profiles of IL-1Ra−− mice fed an HFD.

2. Methods and materials

2.1. Mouse feeding trial

Six-week-old male (C57BL/6) wild-type (WT) and IL-1Ra−− mice were fed an HFD for 16 weeks. HFD consisted of 60% kcal from fat (54% SFA, 6% polyunsaturated), 10% kcal from carbohydrate (15% monounsaturated, 76% sucrose) and 28% kcal from protein (18.7% casein, 0.5% carnitine) as described by the authors [23]. C57BL/6 mice were obtained from Harlan ICL, and breeding pairs of IL-1Ra−− were purchased from Jackson Labs and kept at Trinity College Dublin under specific pathogen-free conditions. Ethical approval for the study was obtained from the Trinity College Dublin Ethics Committee. Mice were maintained according to the regulations of the European Union and the Irish Department of Health. Male mice were studied to avoid potential confounding gender-specific effects. Prior to sacrifice, mice were fasted overnight for 10 h.

2.2. Plasma markers of metabolic health

Plasma markers (fatty acids, triglycerides, lipoprotein [apoB] [apoB]) and nonesterified fatty acids (NEFAs) were measured using a commercial enzymatic assay on a Beckman CX2 analyzer (Beckman Coulter). Blood concentrations were measured using a rat-specific enzyme-linked immunosorbent assay (ELISA Kit, Merck, Chicago, IL, USA). Blood was obtained from the caudal vein of mice by Evans blue injection and analyzed by high-performance liquid chromatography (HPLC) for fasting NEFA levels. Blood glucose was measured using a Beckman Glucose Analyzer (Beckman Coulter).

2.3. Aorta extraction, microarray hybridization, quality control and differential expression analysis

RNA from six WT and six IL-1Ra−− mice was extracted from epididymal adipose tissue using the mirVana platform. For analysis, we used the ensembl version 110.0 annotation from the GenBank genome database (http://ensembl.org/index.html) (Ensembl), which reflects the latest remapping of Affymetrix probes based on data in the July 2010 release of the NCBI database [24]. Raw microarray data were first quality checked using a set of standard QC terms, including array intensity distribution, positive and negative signal element distribution, CTDH2 and -ctn 3' UTR, center of intensity and assay array correlation check. QC terms were implemented in the R programming language [25], using the BioConductor library [26] and all arrays passed QC. After quality assessment, all intensity values were background corrected and normalized using the CEPH3Nq LOW method (i.e., using the EMMIX-BEST argument in the gma function, which uses a slower and more exact optimization algorithm) [27]. Normalized expression values were assessed for differential expression between wild type (WT) and IL-1Ra−− adipose tissue using linear regression and empirical Bayes estimation as implemented in the limma library in R [28]. Significance threshold for all reported single gene changes was set at FDR < 0.05.

2.4. Metabolic network analysis

We used a recently reconstructed [29] metabolic network containing 8554 metabolic reactions and 1212 metabolites after removal of low expression metabolites [30]. In its native form, this reconstruction is a metabolite-centered network (i.e., nodes represent metabolites, and edges are the enzymes that catalyse reactions between them). For our work, we transformed this network into an enzyme-centered network, where genes are listed if gene 1 produces a metabolite (through metabolic conversion) that is used as a metabolite substrate by gene 2.

2.5. Assessment of gene-gene co-expression in the metabolic network

Co-expression was assessed for each gene-gene pair in the metabolic network reconstruction using Arabidopsis thaliana’s information criterion (AIC), an index used for selection of the optimal model among competing possibilities [31]. Gene pairs were assessed for co-expression among WT and knockout mice. As our network reconstruction contains directional information, co-expression between two genes was assessed using a linear model of gene 1 expression as a function of gene 1 expression. Our approach allows for selection of the optimal model among all possible combinations of predictor variables, thus allowing for examination of likelihood values for models of gene 2 expression with and without gene 1 expression as predictors. The chosen value of AIC is determined by

$$ AIC = 2n - 2\ln L $$

where $n$ refers to the number of parameters in the statistical model and $L$ is the maximized likelihood value for the fitted model. An optimal model will balance high likelihood with small number of parameters; therefore, lower AIC values indicate a better model.

### Table 1

**Top regulated genes in adipose tissue of IL-1Ra−− mice relative to WT**

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Name</th>
<th>LogFC</th>
<th>Nominal P value</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pparg3</td>
<td>PPAR3-like phospholipid domain containing 3</td>
<td>3.07014689</td>
<td>1.05E-10</td>
<td>1.85E-06</td>
</tr>
<tr>
<td>1700712a084W</td>
<td>ESR1 (DNA 1700712A08 B1 BLASTZ) gene</td>
<td>-2.7521018</td>
<td>6.02E-06</td>
<td>3.37E-04</td>
</tr>
<tr>
<td>Foxo4</td>
<td>Forkhead box O4</td>
<td>-5.040054</td>
<td>9.20E-07</td>
<td>3.37E-04</td>
</tr>
<tr>
<td>Hsd2l2</td>
<td>17a-hydroxylase and 17,20-lyase</td>
<td>-2.09914712</td>
<td>4.02E-05</td>
<td>1.31E-03</td>
</tr>
<tr>
<td>G6pc2</td>
<td>Glucokinase 2</td>
<td>1.6096169</td>
<td>2.74E-05</td>
<td>2.74E-03</td>
</tr>
<tr>
<td>Mc2r</td>
<td>Melanocortin 2 receptor</td>
<td>2.0815755</td>
<td>2.15E-06</td>
<td>3.86E-05</td>
</tr>
<tr>
<td>Pam</td>
<td>Phosphamidate monoesterase 4, phosphomonoesterase 4, phosphomonoesterase 5</td>
<td>-0.9319638</td>
<td>9.20E-06</td>
<td>3.37E-04</td>
</tr>
<tr>
<td>Gm6</td>
<td>Glutamine dehydrogenase</td>
<td>1.3338728</td>
<td>6.02E-06</td>
<td>3.37E-04</td>
</tr>
<tr>
<td>Socs3</td>
<td>Stat5bsuppressor of cytokine signaling 3</td>
<td>2.28E-06</td>
<td>9.45E-06</td>
<td>1.31E-03</td>
</tr>
<tr>
<td>Iph1</td>
<td>Inositol-phosphate binding protein 3</td>
<td>1.998629</td>
<td>1.29E-05</td>
<td>1.42E-03</td>
</tr>
<tr>
<td>Pdp1a</td>
<td>Phosphatidylserine phosphatase alpha</td>
<td>1.0541646</td>
<td>1.52E-05</td>
<td>1.03E-02</td>
</tr>
<tr>
<td>Pmp1</td>
<td>Membrane protein, member of family 1A</td>
<td>2.01415</td>
<td>2.86E-06</td>
<td>2.07E-04</td>
</tr>
<tr>
<td>1700712a084W</td>
<td>ESR1 (DNA 1700712A08 B1 BLASTZ) gene</td>
<td>-2.7521018</td>
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<td>-2.7521018</td>
<td>6.02E-06</td>
<td>3.37E-04</td>
</tr>
</tbody>
</table>

The table shows genes with FDR < 0.05 after Benjamin and Hochberg correction for multiple testing.
Fig. 1. Plasma levels of inflammatory markers in WT and IL-1β<sup>−/−</sup> C57BL/6 mice fed a high-fat diet for 16 weeks. These markers illustrate distinct features of the proinflammatory phenotype in knockout mice despite the presence of diet-induced obesity.

2.6. Extraction of diet-sensitive paths from a co-expressed network

Directed shortest paths [32] were calculated for each node exhibiting genotype-sensitive expression to all others in the network (i.e., the subset of the global network, consisting only of gene pairs determined to be co-expressed in knockout mice), taking into consideration directionality of node pair interactions. An algorithm was implemented in R to evaluate modularity of each pairwise path — i.e., whether an unbiased path of metabolic conversion could be traced from one end to the other (see Ref. [33] for a more detailed discussion of this method, as well as comparison to standard pathway enrichment analysis).

2.7. Statistical analysis of plasma marker–gene associations

Regressed canonical correlation analysis (RCCA) is a multivariate statistical method used to assess correlations between two multivariate datasets [34] and was used here to assess correlations between plasma markers of metabolic health and gene expression values. The ‘mvrtest’ library of functions in R was used to carry out the analysis [35]. Specifically, the scree test function was used for estimation of regularization parameter, and the test function was used to define the canonical correlations and the canonical variates. Using the network function to produce a network of plasma marker–gene interactions, the first two components and a correlation threshold of 0.7 (i.e., using the ‘comp’ and ‘threshold’ arguments in the network function) were used to select the subset of most strongly correlated pairs.

2.8. Intra-hierarchy protein–protein interaction (PPI) regulatory network analysis

A PPI network was reconstructed using all 3,914 Mus musculus-specific interactions in the IntAct (www.intact-db.org) — a manually curated database describing PPI and regulatory interactions relating to innate immunity [36]. The resulting network contained 818 genes and 952 proteins. This network was then assessed for modularity, which is a network property that describes the optimal partition of the network into individual subnetworks (i.e., modules) wherein the number of within-module links is maximized and between-module links are minimized. Modules (or, in this case, semi-independent structural components of the network) were further discussed as modular structure in protein interaction networks, see Gurvits et al. [37]. The largest connected component of the network was partitioned into modules using the complementarity function in the graph library in R. Each module was tested for significant enrichment of IL-1β<sup>−/−</sup>-sensitive genes using an adapted version of gene set enrichment analysis [38].

3. Results

3.1. Analysis of gene expression and correlation with plasma markers

IL-1β<sup>−/−</sup> and WT mice were fed an HFD for 16 weeks, and gene expression profiles were analyzed using Affymetrix microarrays. Comprehensive phenotype data have been presented previously [23]. Briefly, food intake did not differ between the intervention groups (data not shown), and both groups gained similar body weight over the course of the intervention (10.5 ± 3.8 g in IL-1β<sup>−/−</sup> mice and 18.5 ± 0.9 g in control mice, P < 0.05). Single gene expression analysis of the microarrays highlighted 25 genes with significantly different expression between the genotype groups after correction for multiple testing using the approach proposed by Benjamini and...
Hochberg (39) (1579 significantly regulated genes according to nominal P values) (Table 1). The most significantly up-regulated genes in IL-1β- relative to WT included Aplex2, an adipocyte-specific lipolysis gene, and Cyp2, an enzyme that links macrophage metabolic pathways through reversible conversion of alanine and 2-oxoglutarate to form pyruvate and glutamate. Also among the top regulated genes were Glut2, Socs1, and Cyp2j6, which are involved in oxidation reduction, and two isoforms of G-protein-coupled receptor (Cgr1, Cgr1b) — a family of proteins with roles in immune system regulation. The most significantly down-regulated genes included Prdx2, an enzyme involved in redox regulation with a role in T-cell activation, and Ptx3, which plays a regulatory role in the phosphoinositide 3-kinase complex. Quantitative reverse transcriptase polymerase chain reaction validation of microarray expression demonstrated agreement in direction of change for 11 of 12 targets (Supplementary Fig. S1). In conjunction with the attenuated inflammatory profile, adipose GLUT4 mRNA was increased in IL-1β-/- mice (Supplementary Fig. S1), indicative of improved glucose homeostasis.

A significant reduction of plasma TNFα and IL-6 concentrations, coincident with greater adiponectin concentrations in IL-1β-/- mice (Fig. 1), showed interesting relationships with the adipose

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**Fig. 2** Transcriptionally coordinated gene sets. Blue nodes: down-regulated genes, yellow nodes: up-regulated genes; red nodes: plasma markers. Wavy lines indicate negative plasma marker-gene correlations; dotted gene-gene connections indicate gene pairs that are positively coexpressed in IL-1β-/- mice but not in WT mice. (A) Path linked to lpplp; (B) path linked to ly6c; (C) path linked to fn3f.
transcriptome — as identified by rCCA. Fig. 2 indicates that, of all plasma markers included in the analysis, plasma TNFα and IL-6 correlated most strongly with adipose tissue gene expression. At the chosen thresholds, 44 genes correlated with plasma TNFα — 22 negatively and 22 positively. Plasma IL-6 concentrations showed positive correlation with seven genes and negative correlation with five. The strongest plasma marker-gene correlations were between TNFα and Cc03, Asl and C16h.

3.2. Genotype-sensitive co-expressed paths in the metabolic network

Extraction of co-expressed, metabolically feasible paths linked to upstream genotype-sensitive genes (i.e., genes with nominal P value < .05 from the above differential expression analysis) identified 48 unique paths with length ≥3. A subset of these paths, selected based on high proportion of genotype- and plasma marker-correlated genes, is shown in Fig. 3. The path in Fig. 3A contains key reactions involved in lipolysis and triglyceride formation. Ppap2a produces diacylglycerol (DAG) through metabolic conversion of phosphatidate.

This DAG is further metabolized by Dgko and Dgkd to form phosphatidic acid, by G6d and Plpm3 to form monoaclglycerol and fatty acids, and by G6d1 and Dgkd2 to form TAG. Both Ppap2a and Plpm3 were up-regulated in the knockout mice and were shown in the rCCA results to be inversely correlated with plasma TNFα. Plpm3 was also negatively correlated with plasma IL-6. Furthermore, all enzyme pairs in this path were positively co-expressed in the knockout mice, indicating increased coordination in genes related to fatty acid and triglyceride cycling.

Fig. 3B shows a co-expressed path linked to Cyp7a1, an enzyme that reversibly produces oxaloacetate and acetyl-CoA from citrate. These and the remaining metabolites and enzymes in the path are part of the tricarboxylic acid (TCA) cycle — with the exception of IDP, which links the TCA cycle to purine metabolism. Of the 21 genes in this path, 6 were significantly up-regulated in IL-1β1/−/− mice (Cylm, Pck1, Cpi2, Ppat1, Dist, Altz2), and 2 showed inverse correlation with plasma levels of IL-6 (Pck1, Cpi2). Fig. 3C shows the path linked to Fdrl, which acts on tetrahydrofolate to form l-glutamate and 10-formyltetrahydrofolate. The Fdrl-linked path contains 16 genes, of which 7 were

Fig. 4: Modular partition of Immunity network of innate immunity. Yellow nodes: up-regulated genes (nominal P value < .05); blue nodes: down-regulated genes. (A-C) Detailed views of modules showing significant enrichment for IL-1β1/−/− genes.
down-regulated (P<0.01; GI50<1000). Figs Hpd, Cyp3A11, and 1 was up-regulated (P<0.01) in the IL-1R1−/− mice. Plasma TNFα levels correlated with expression of Figs and Cyp3A11, and IL-6 with Hpd. Interestingly, both the PdcD- and Cyp3A11-linked pathways contain 2-oxoglutarate, succinate, and 2-oxoglutarate metabolites. However, they are metabolized by different enzymes in the two pathways, reflecting alternate pathways of conversion for a given metabolite. In the case of 2-oxoglutarate and 2-oxoglutarate, the implicated enzymes are up-regulated in the Cyp3A11-linked pathway and down-regulated in the PdcD-linked path.

3.3 Enriched modules in the innate immunity IPI/regulatory network

Modular decomposition of the largest connected component of the innate immunity IPI/regulatory network identified 30 modules, ranging in size from 3 to 82 nodes (Fig. 4; modules 3 to 30 are described in Table 2). For all except one module, intramodule links exceed extramodule links. Analysis of statistical enrichment of each module for IL-1R-sensitive genes indicated three significantly enriched modules (nominal significance threshold <0.01; Table 2, Fig. 4). The first of these three modules, module 11, showed significant bidirectional enrichment (i.e., enrichment for both up- and down-regulated genes). Closely inspection of gene content in this module showed a predominance of transcription regulation interactions between Stat3 and many target genes of this transcription factor (Fig. 4A). Although Stat3 showed only a near-significant trend toward down-regulation in IL-1R1−/− (nominal P=0.06), 10 Stat3 target genes in module 11 were significantly regulated. Assessment of all nodes in the innate immunity network identified an additional five significantly regulated Stat3 targets.

Module 15 was shown to be significantly up-regulated (Fig. 4B). This module contained Map3k1, Map3k9, and Map3k10 (which collectively encode the JNK protein) as well as Slc20a4 (Glu4, which encodes glucose carrier protein). Significantly up-regulated genes in module 15 included Mapk9, Slc20a4, and Ijup (tumor necrosis factor protein). Module 27, which was primarily composed of interaction partners of IL-1β, was also significantly enriched (Fig. 4C). Although only one gene — P68 — was significantly regulated in this module, an additional four genes (Sphe1, Rsa1, Pan, Hmga2) showed near-significant regulation (FDR <0.05), which likely explains the overall significant result in the module.

4. Discussion

Adipose tissue inflammation is now recognized as a central player in the etiology of HFD-induced IR [4]. Metabolic network analysis of transcriptomic effects identified up-regulation and co-expression of genes involved in lipolysis, lipogenesis, and TCA cycle, coinciding with an attenuated plasma inflammatory cytokine in HFD fed IL-1R1−/− mice relative to weight-matched HFD-fed wild-type mice. Further assessment of gene expression in a network of protein interactions related to innate immunity highlighted Stat3 as a potential transcriptional regulator of IL-1 signaling. These findings add to recent work by our group, demonstrating that lack of IL-1β protected mice from HFD-induced adipose tissue inflammation and IR, an effect that was mediated by lower p-STAT3 signaling [11].

Adipose tissue gene expression analysis revealed significant changes in lipid metabolism in the knockout mice. The most significantly up-regulated gene was a lipolysis enzyme (Ppap2c); metabolic network analysis further identified a co-expressed subnetwork involved in both lipolysis and lipogenesis that showed increased activity in IL-1R1−/− mice. The critical importance of lipogenesis in adipose tissue is highlighted by the adipose tissue expandability hypothesis, which proposes that impairment of fat storage capacity in adipose tissue leads to fatty acid accumulation and subsequent lipotoxicity in other tissues [40]. Furthermore, the lipid metabolism intermediate molecule DAG activates proinflammatory protein kinases such as mTOR, PKC, JNK, P38, and the MAP kinase family — confounding the pathology of impaired fat storage and storage of lipids [1]. Fig. 5A illustrates up-regulation of genes involved in production of DAG (Ppap2c) and conversion of DAG to fatty acid (Ppap2c) in IL-1R1−/− mice. Furthermore, positive co-expression between Ppap2c and Dag2 in knockout mice indicates a potential increase in DAG clearance through DAG production. Overexpression of Dag1 in adipose and muscle tissue and Dag2 in liver tissue has been shown to protect against high-fat-induced IR [42–44], though neither Dag1 nor Dag2 expression was significantly different between genotype groups. Dag1 showed a nonsignificant trend toward up-regulation in knockout mice (nominal P=0.058). Furthermore, increased co-expression between Dag1/2 and Ppap2c in knockout mice suggests a possible activation of a common transcription regulator. Given the importance of lipogenesis and DAG clearance in the context of inflammation and IR, this subnetwork represents a functionally relevant target for future work.

Co-expression analysis in the metabolic network also identified a path of enzymes involved in the TCA cycle (Fig. 3B). The clinical relevance of TCA activity has been demonstrated in T2DM patients, where reduced flux in the TCA cycle was observed in diabetic muscle tissue, relative to lean controls [45,46]. In adipose tissue of diabetic humans, synuclein insulin sensitivity through the mitochondrial treatment increases expression of TCA cycle genes [47]. By extension, increased substrate accumulation, as observed in T2DM, should correlate with decreased TCA activity. While few studies have explicitly explored this link, particularly with regard to IL-1, a recent study of IL-6-deficient mice fed an HFD reported substantial induction of a hepatic inflammation paired with coordinated down-regulation of TCA-related genes [48].

These findings on lipid metabolism and TCA cycle activity are in line with the broader observation of mitochondrial dysfunction in IR
and TNF-α [49]. High fat intake is directly related to mitochondrial dysfunction. It has been proposed that increased fatty acid β-oxidation without concomitant up-regulation of TCA cycle activity leads to increased oxidation and accumulation of lipid-derived intermediate metabolites [50]. Accordingly, restoration of TCA cycle activity through exercise in HFD-fed mice positively correlates with a decrease in fasting glucose [51]. An up-regulation of TCA enzymes observed in the LIR-IR mice may therefore indicate a degree of restoration of mitochondrial function, although it is likely that these observed changes could be partly explained by increased basal uptake in adipose tissue.

Analysis of a PPI/regulatory network of innate immunity reactions identified a significantly enriched module composed primarily of transcriptional targets of the Stat3 transcription factor. Stat3 is induced by proinflammatory cytokines such as IL1 and also a central regulator of adipogenesis [52]. Stat3 target genes shown to be significantly up-regulated in the LIR-IR mice included Snf5 (a gene involved in GLUT4 processing) [53], and Cpg4, which may also play a role in adipocyte differentiation [54]. In addition to these changes within the interaction network, the key adipogenic transcription factors Pparg and FoxO were all up-regulated in the kitted mice. Such changes in adipogenic genes may be functionally relevant to observed up-regulation of GLUT4. A direct link between adipose tissue expansion and IR has been demonstrated in genetic mouse models with altered adipose tissue development. The F4/80+ mouse shows diminished ability to form adipose tissue and displays an IR phenotype even more severe than the commonly used obese mouse model of obesity-induced IR [55]. In addition to this, the AgRP/ob Agouti mouse model — which overexpresses adiponectin — possesses substantially enhanced ability for adipose tissue expansion and exhibits insulin sensitivity despite obesity [56]. Taken together, our observations and growing evidence in lipogenesis and plasma adiponectin suggest that it is possible that the hallmark features of IR mice show similarly increased adipogeneic capacity. Indeed, LIR-IR mice fed a chow diet have a tendency towards spontaneous obesity in later life [58]. However, this theory is complicated by the parallel increase in the lipolytic gene Pparg and lack of variation in body weight between the genotype groups.

In summary, we have used two distinct network analyses of transcriptional data to identify metabolic and regulatory consequences of IL-1β-mediated signalling in HFD-fed mice. DAG metabolism and TCA cycle were up-regulated in IL-1β' mice, suggesting potential changes in adipogenesis and mitochondrial function. Furthermore, Stat3, Ppargc1a, Ror2, and Ireg1 were highlighted as potential IL-1β-dependent regulators of adipogenesis in the context of HFD and this represent functional targets for future studies of IL-1β-mediated activation and subsequent inflammation.

Supplementary data to this article can be found online at [link].

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References


