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Review article

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Emerging mechanisms of obesity-associated immune dysfunction

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Abstract

Obesity is associated with a wide range of complications, including type 2 diabetes mellitus, cardiovascular disease, hypertension and nonalcoholic fatty liver disease. Obesity also increases the incidence and progression of cancers, autoimmunity and infections, as well as lowering vaccine responsiveness. A unifying concept across these differing diseases is dysregulated immunity, particularly inflammation, in response to metabolic overload. Herein, we review emerging mechanisms by which obesity drives inflammation and autoimmunity, as well as impairing tumour immunosurveillance and the response to infections. Among these mechanisms are obesity-associated changes in the hormones that regulate immune cell metabolism and function and drive inflammation. The cargo of extracellular vesicles derived from adipose tissue, which controls cytokine secretion from immune cells, is also dysregulated in obesity, in addition to impairments in fatty acid metabolism related to inflammation. Furthermore, an imbalance exists in obesity in the biosynthesis and levels of polyunsaturated fatty acid-derived oxylipins, which control a range of outcomes related to inflammation, such as immune cell chemotaxis and cytokine production. Finally, there is a need to investigate how obesity influences immunity using innovative model systems that account for the heterogeneous nature of obesity in the human population.

Sections

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Key points

- Obesity dysregulates immunity through differing mechanisms, which contribute to a range of secondary complications.
- Obesity influences the level and function of nutritionally regulated hormones that regulate signalling pathways that mediate immune cell metabolism and function and drive inflammation.
- Expansion of adipose tissue dysregulates the abundance and composition of extracellular vesicles, which carry a wide range of cargo that can affect the activity of immune cells and lipid metabolism.
- Increased adiposity dysregulates polyunsaturated fatty acid metabolism; notably, the concentration of oxylipins synthesized from polyunsaturated fatty acids, which control a range of outcomes related to inflammation, is imbalanced in obesity.
- Investigating immunity in obesity requires translation from inbred rodents to humans; one approach is to use Diverse Outbred and Collaborative Cross mouse populations that can model the heterogeneous nature of human obesity.

Introduction

Obesity is defined by the WHO as 'excessive fat accumulation that presents a risk to health, with a BMI >30 kg/m^2'; it affects more than 40% of adults in the USA and is increasing in prevalence worldwide[1]. Obesity is a highly heterogeneous disease, the aetiology of which is varied but includes environmental factors (for example, access to healthy food, exposure to environmental pollutants), lifestyle (for example, physical activity, overnutrition, alcohol consumption, stress) and predisposition (for example, underlying microbiome profile, hormonal control, genetics, epigenetics)[2–4].

Obesity can give rise to a wide range of complications, such as type 2 diabetes mellitus, nonalcoholic fatty liver disease, cardiovascular disease, increased incidence of various cancers, poor responsiveness to infections and vaccines, and neurodegenerative disorders. There is a crucial need to understand how obesity drives these numerous complications. Dysregulation of innate and adaptive immunity leading to chronic, low-level, tissue-specific and systemic inflammation is one major factor that contributes towards the progression of many obesity-related disorders and metabolic diseases, such as insulin resistance leading to type 2 diabetes mellitus[5]. Obesity has also been shown to increase morbidity and mortality associated with certain infections, such as influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Specifically, individuals with obesity are more likely than individuals with a BMI in the normal range to be hospitalized, admitted to intensive care units, require mechanical ventilation and die from coronavirus disease 2019 (COVID-19)[6–11]. In addition, obesity-driven impairments in the response of select adaptive immune cells lead to poor immune memory responses, as exemplified by impaired vaccine responsiveness, which is further exacerbated by age[12,13]. Adults with obesity have impaired influenza vaccine responsiveness and, compared with adults without obesity, showed double the risk of influenza infection, despite vaccination[14]. There is also compelling evidence that crosstalk between epithelial cells, specific immune cells and adipocytes occurs in response to obesity-associated hormonal signalling, which, in the context of breast cancer, increases the risk and/or progression of disease[15]. Thus, the innate and adaptive immune systems are major targets for therapeutic interventions that mitigate the impact of obesity.

This Review outlines emerging cellular and molecular mechanisms by which obesity impairs key aspects of immunity. First, we provide an overview of how obesity-driven changes in the abundance of key hormones dysregulate immunometabolism and promote inflammation. We then discuss advances in our understanding of how adipose-tissue-derived extracellular vesicles regulate immune cell phenotypes and how these processes become dysregulated upon expansion of adipose tissue. We also outline how expansion of adipose tissue dysregulates polyunsaturated fatty acid (PUFA) metabolism, with a specific focus on the action of PUFA-derived oxylipins that control molecular pathways related to inflammation. Finally, we conclude with the viewpoint that future studies focused on the links between obesity and immunity will need to account for heterogeneity in the human population to effectively translate therapeutics from preclinical studies to the clinic.

Obesity and immunometabolism

The metabolism and function of immune cells are closely related, and changes in cellular metabolism can impact immune cell responses in both health and disease. This interplay between immune cell metabolism and function has been well described in T cells, B cells, macrophages and dendritic cells[16–23]. For example, naive, memory and regulatory T (T_{reg}) cells rely heavily on oxidative metabolism to fuel their immune surveillance and suppressive functions, whereas activated effector T cells use increased glucose and glutamine uptake and increased aerobic glycolysis to fuel their effector functions and produce the biomass needed for growth and proliferation, with nuances and differences in the metabolic programmes of different effector T cell subtypes[16,17,24]. Similarly, classically activated 'pro-inflammatory' M1 macrophages show increased glycolytic metabolism, which promotes the production of pro-inflammatory cytokines and phagocytosis, whereas alternatively activated 'anti-inflammatory' M2 macrophages show increased mitochondrial respiration, which promotes the production of anti-inflammatory cytokines that help with wound healing and tissue repair[21,22].

Obesity dysregulates immune cell metabolism. For example, it is well established that obesity leads to the accumulation in visceral adipose tissue of pro-inflammatory immune cells, including macrophages and lymphocytes, with high levels of nutrient metabolism, which drive low-grade inflammation, promoting metabolic disease[25]. Additional studies have shown that obesity also induces metabolic changes in circulating immune cells. For example, CD4$^+$ T cells isolated from C57BL/6J mice with obesity induced by a high-fat diet showed increased glucose uptake and an increased oxygen consumption rate (OCR; a surrogate for mitochondrial oxidation) but no change in extracellular acidification rate (ECAR; a surrogate for lactate production) when activated in vitro, resulting in an increase in the OCR to ECAR ratio[26]. This unique cellular metabolic phenotype of increased glucose oxidation is not used by naive, memory or activated T cells from lean animals and could mechanistically explain obesity-associated T cell dysfunction. In support of these in vitro findings, similar changes in peripheral T cell metabolism were observed in obese mice in vivo after either primary influenza infection or influenza re-infection. Importantly, this metabolic phenotype was associated with T cell dysfunction, leading to decreased T cell memory in the re-infection model[27] and increased mortality from influenza in the primary infection model[26]. In a separate study, CD8$^+$ T cells isolated from the lungs of obese mice

after influenza infection were metabolically and functionally impaired compared with $CD8^+$ T cells from lean mice[28]. Another study in mice with obesity induced by a high-fat diet showed increased differentiation of pro-inflammatory T helper 17 (T_H17) cells as well as increased T_H17 cell pathogenicity compared with mice fed a normal diet; both increases were mediated through the induction of the lipid metabolic kinase acetyl-CoA carboxylase[29]. Additional work has confirmed the predominance of peripheral T cell inflammation, particularly T_H1 and T_H17 cell responses, in driving obesity-associated metabolic disease in human studies[30].

To target and treat obesity-related immune dysfunction, it is important to understand how obesity alters immune cell metabolism and function. In the following sections, we outline emerging mechanisms by which obesity might influence key aspects of immunity.

Nutritionally regulated hormones

One potential mechanism involves changes in the hormones that communicate nutritional status to immune cells. Several nutritionally regulated hormones have pleiotropic roles, regulating both systemic metabolism (for example, appetite, energy expenditure, body adipose tissue distribution) and immune cell metabolism and function[31,32]. Here, we discuss select examples of such hormones, which include leptin, insulin, insulin-like growth factor 1 (IGF1) and glucagon-like peptide 1 (GLP1).

Leptin. Leptin is a nutritionally regulated hormone that is secreted from adipocytes in quantities proportional to adipocyte mass; levels of leptin are therefore increased systemically in individuals with obesity compared with those without obesity. Although leptin is best known for its role in regulating appetite and energy expenditure and thereby controlling body weight through signalling to the hypothalamus, it is also an immune regulator[33]. Multiple studies show that leptin regulates almost every cell of the immune system, including innate and adaptive immune cells, but potently influences $CD4^+$ T cells[33]. Humans with mutations in the genes that encode leptin or the leptin receptor have been identified and found to have $CD4^+$ T cell immunodeficiency, leading to an increased risk of intracellular infections[34–36]. In the case of leptin deficiency, both systemic metabolism and immunity were normalized following treatment with recombinant leptin[37]. These findings in humans have been confirmed in mouse models of leptin deficiency (*ob/ob* mouse)[38] and leptin receptor deficiency (*db/db* mouse)[39]; notably, these mice also show multiple immune cell abnormalities that lead to increased susceptibility to infections, alongside protection against select autoimmune diseases.

Although many of the effects of leptin on immunoregulation have been described in the context of T cells, leptin also influences B cells and innate immune cell responses[33,40,41]. Some of the effects of leptin on B cells might be mediated through T follicular helper (T_{FH}) cells (a specialized subset of $CD4^+$ T cells), as leptin has been found to promote the differentiation and function of T_{FH} cells (through STAT3 and mammalian target of rapamycin (mTOR) signalling pathways) to support antibody responses in mouse models of both infection and vaccination[42]. Moreover, leptin has been found to promote antitumour immunity in obesity by inducing the polarization of tumour-associated macrophages towards an M1, pro-inflammatory phenotype[43].

One key mechanism by which leptin affects T cell responses is through changes in cellular metabolism. Indeed, leptin signalling is required for increased glucose uptake, glycolysis and mitochondrial respiration following activation of effector T cells (T_H1 and T_H17) but not T_{reg} cells, in a cell-intrinsic manner, via upregulation of the glucose transporter GLUT1, a crucial regulator of T cell glucose metabolism[44,45]. In a mouse model of autoimmunity, leptin deficiency was found to decrease the expression of the glycolytic enzyme hexokinase 2 as well as the glycolytic regulator hypoxia-inducible factor 1 (HIF1)α in T_H17 cells, but not T_{reg} cells, indicating a crucial role for leptin in promoting inflammatory T cell metabolism and function in the context of autoimmunity[45].

Insulin and IGF1. Insulin is another example of a nutritionally regulated hormone that affects immune cell function. Insulin is secreted from pancreatic β-cells proportionally in response to blood glucose levels and is best known for its role in promoting glucose uptake in skeletal muscle, liver and adipose tissue by increasing expression of the glucose transporter GLUT4. Insulin also has well-known effects on fatty acid and amino acid metabolism and is therefore a crucial regulator of both systemic and cellular metabolism. Circulating levels of insulin are increased in obesity owing to obesity-associated peripheral insulin resistance[46].

Insulin is a key regulator of immune cells, with the ability to modulate immune cell differentiation and function[47], particularly of $CD4^+$ T cells[48,49]. Using rat and mouse models of insulin receptor deficiency, insulin receptor signalling was found to be crucial for the regulation of both metabolism and function of T cells, in a subset-dependent manner, with consequences of receptor deficiency on autoimmune disease, inflammation and viral response[50,51]. Similar to leptin, the effects of insulin on T cell function are mediated through changes in cellular metabolism — via regulation of glucose uptake and amino acid transport[51], with increased mitochondrial respiration reported in $CD4^+$ T cells[52].

IGF1 has a similar sequence and structure to pro-insulin, and both the insulin receptor and the IGF1 receptor belong to the same family of tyrosine kinase receptors. Both receptors thus induce similar downstream signalling pathways that involve AKT and mTOR, which are well-known regulators of cellular metabolism and function. The bioavailability of IGF1 is regulated by insulin-like growth factor binding proteins (IGFBPs) and, as such, IGF1 bioavailability is regulated by dietary protein intake; levels of free IGF1 are elevated in obesity owing to decreased levels of IGFBPs[53–56].

IGF1 has a role in T cell development and function and has been identified as a potent regulator of T_H17 cell function and metabolism via mTOR signalling[57]. IGF1 has also been found to increase mitochondrial oxidation in $CD4^+$ T cells, particularly T_H17 cells, while decreasing mitochondrial membrane potential and mitochondrial reactive oxygen species via uncoupling protein 2, thereby ascribing a cytoprotective effect to IGF1 on T_H17 cells[52]. This cytoprotective effect is relevant in obesity, as peripheral T cells, including T_H1 and T_H17 cells, have been shown to dominate peripheral inflammation in human obesity[30], indicating that increased levels of IGF1 might be important in driving obesity-induced inflammation in humans. Other studies have identified a role for IGF1 in macrophage function and metabolism, and myeloid-specific ablation of the IGF1 receptor in mice fed a high-fat diet resulted in reduced myeloid cell phagocytosis, increased numbers of macrophages in adipose tissue and increased insulin resistance, indicating additional roles for IGF1 in driving obesity-associated inflammation and metabolic disease in the mouse model[58]. Given the structural similarity between insulin and IGF1 and the shared receptor family, it is not surprising that IGF1 is also emerging as an important regulator of immune cell metabolism and function.

Targeting leptin, insulin and IGF1. Despite a clear role for leptin, insulin and IGF1 in regulating immune responses (Fig. 1), two key aspects make these hormones and their receptors problematic candidates for therapeutic targeting. First, the hormones have pleiotropic and complex roles in obesity, inflammation, response to infection and autoimmunity that are often context dependent. For example, several studies have identified roles for leptin, insulin and IGF1 in the setting of obesity-specific tumour immunity. As mentioned above, leptin has been found to augment antitumour immunity by repolarizing tumour-associated macrophages[43], and it has been suggested that leptin might have a role in promoting the effectiveness of tumour-infiltrating lymphocytes in patients with overweight or obesity and breast cancer[59]. Some studies have also identified a favourable, antitumour, role for leptin in pancreatic cancer, colorectal cancer and melanoma; however, other studies have identified leptin as a poor prognostic factor[60]. In addition, dietary interventions, such as calorie restriction and short-term fasting, have been shown to decrease tumour growth in mouse models, which has been attributed to decreased insulin and IGF1 levels, leading to decreased growth signalling as well as enhanced tumour immunity[61,62]. However, in a mouse model of obesity, weight loss was unable to normalize adipose inflammation, reverse altered T cell metabolism or improve the impaired immune response to influenza infection, despite normalization of systemic insulin and leptin levels[27].

The second aspect is the Goldilocks principle: that leptin, insulin and IGF1 signalling to immune cells needs to be 'just right'. 'Too little' signal prevents effective immune responses, whereas 'too much' causes immune dysfunction. These challenges point to the importance of identifying therapeutic targets downstream of nutritionally regulated hormones and their receptors, such as signalling and metabolic proteins, to target these signals in a cell-specific manner.

Notably, although insulin and leptin resistance have been described in obesity, with insulin resistance occurring in metabolically active cells and tissues and leptin resistance occurring in the hypothalamus, there is no clear evidence that leptin or insulin resistance occurs in immune cells in the setting of obesity. What is clear, though, is that the effects of these nutritionally regulated hormones on immune cells in obesity are complex and context dependent.

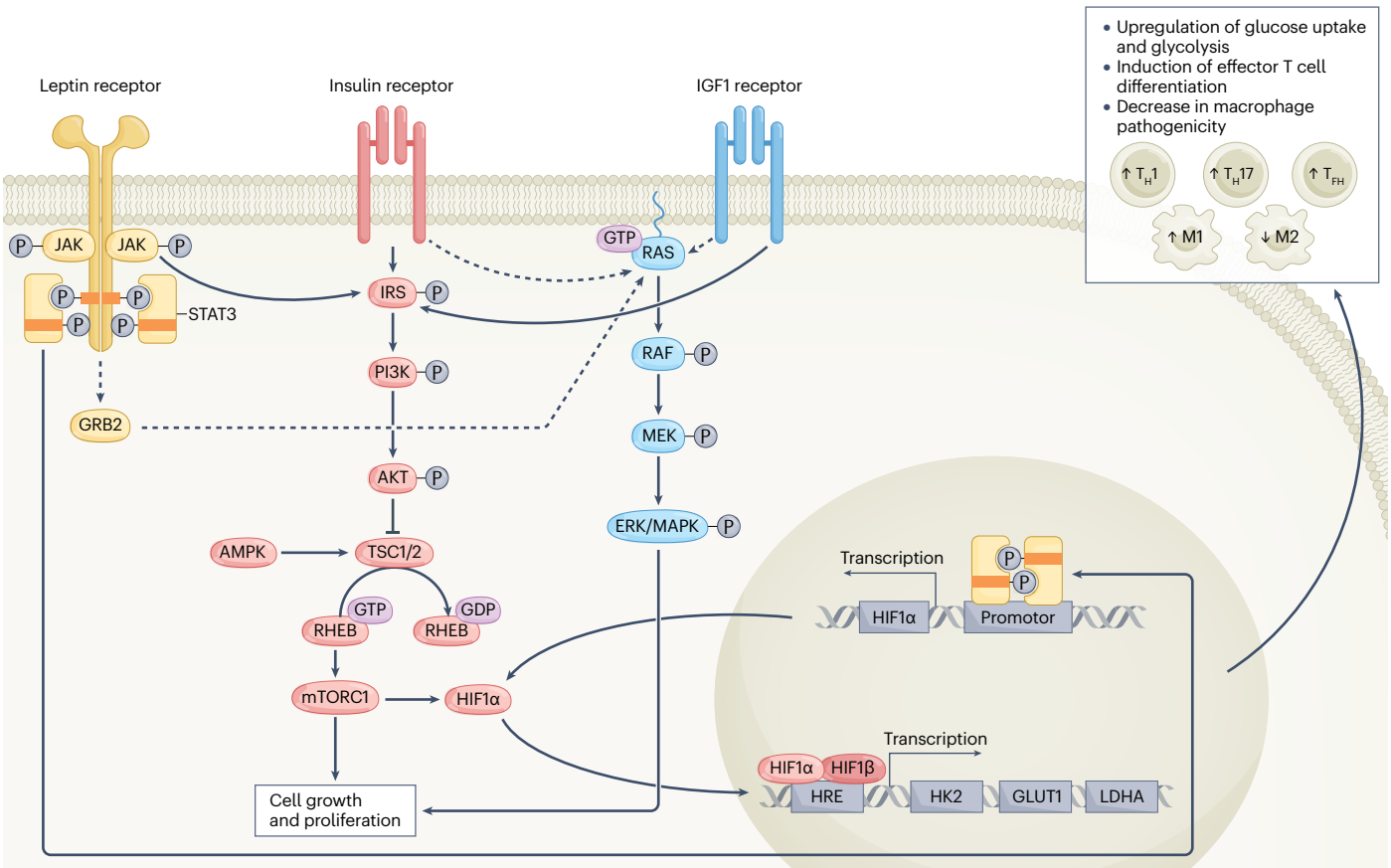

Fig. 1 | Summary of obesity-associated hormone signalling and the regulation of immunometabolism and immune function. Leptin, insulin and insulin-like growth factor 1 (IGF1) binding to their receptors induces signalling through the extracellular-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) and AKT–mechanistic target of rapamycin complex 1 (mTORC1) pathways, leading to cell growth and proliferation. mTORC1 also activates hypoxia-inducible factor 1α (HIF1α), and the expression of HIF1α can also be induced by leptin through JAK–STAT signalling; HIF1α induces the expression of several genes with protein products that are involved in glycolysis. At the cellular level, these changes in gene expression promote effector T cell and M1-like macrophage differentiation. Glucagon-like peptide 1 signals differently and is therefore not depicted here. AMPK, 5′ AMP-activated protein kinase; GRB2, growth factor receptor bound protein 2; HRE, hormone response element; IRS, insulin receptor substrate; LDHA, lactate dehydrogenase A; M2, M2-like macrophage; P, phosphate; PI3K, phosphatidylinositol 3-kinase; T_{FH}, T follicular helper cell; T_H1, T helper 1 cell; TSC, tuberous sclerosis complex.

GLP1. Another nutritional hormone with an emerging role in the regulation of immunity is GLP1. GLP1 is a peptide hormone secreted by epithelial endocrine L cells in the gastrointestinal tract after food consumption. GLP1 is an incretin, which means it regulates the secretion of insulin following an oral glucose load (that is, a meal) in a glucose-dependent manner by signalling through GLP1 receptors expressed on pancreatic β-cells. Many patients with obesity are prescribed GLP1 receptor agonists (GLP1RAs) to treat type 2 diabetes mellitus and/or promote weight loss. Commonly used GLP1RAs include exenatide, dulaglutide, liraglutide and semaglutide. In particular, liraglutide and semaglutide share close peptide homology with GLP1.

Numerous studies have highlighted an anti-inflammatory role for GLP1RAs, with potential effects on both innate and adaptive immune cells. For example, GLP1RAs have been shown to decrease macrophage inflammation in vitro[63], as well as reduce inflammation and improve survival in multiple animal models of sepsis[64–67]. Several studies have also shown an anti-inflammatory role for GLP1RAs in T cells: GLP1RAs can inhibit the proliferation of T_H1 and T_H17 cells in vitro[68], increase the number of T_{reg} cells in vivo[69] and inhibit $CD4^+$ T cell inflammation in several animal models of disease in vivo, such as hepatosteatosis[70], multiple sclerosis[71] and nephritis[68]. GLP1RAs also decrease the expression of GLUT1 and glycolysis in T cells[68], providing evidence that the effects of GLP1RAs on T cells might be mediated metabolically. In 2022, GLP1RA treatment was found to reduce T_H17 cell infiltration of pancreatic islets and restore the T_H17–T_{reg} cell balance in the *db/db* mouse model of obesity and diabetes, thereby alleviating islet inflammation[72]. Altogether, this highly popular class of drugs prescribed to treat obesity and diabetes mellitus might have favourable anti-inflammatory effects that make these drugs attractive as a therapeutic option for multiple indices of health and obesity-associated disease.

Extracellular vesicles

Another emerging mechanism by which nutritional status can be communicated to immune cells is through extracellular vesicles (Box 1).

Box 1

Extracellular vesicles

Extracellular vesicles are submicron bilayer-enclosed particles, secreted by nearly all cells, that have a crucial role in cell–cell communication. Extracellular vesicles are broadly categorized as exosomes, microvesicles and apoptotic bodies. Exosomes are small vesicles, approximately 30–150 nm in diameter, that are formed in endosomes and released upon fusion with the cellular plasma membrane. Microvesicles are approximately 100–1,000 nm in diameter and are synthesized from the processes of plasma membrane budding. Apoptotic bodies constitute the largest class of extracellular vesicle; they are generated during apoptosis and are relatively large (>5 μm in diameter). Extracellular vesicles contain a wide range of cargo, reflecting their source of secretion, including proteins, nucleic acids, lipids and other molecules. The abundance and cargo of a given extracellular vesicle is specific to each cell type. Extracellular vesicles are also of interest from a drug delivery perspective.

Extracellular vesicles are nano-sized vesicles released from various cells, including adipocytes, hepatocytes and immune cells. These bilayer vesicles, which range in size from 50 to 1,000 nm, can contain receptors, transcription factors, proteins, lipids, enzymes and nucleic acids. Upon reaching a target cell, extracellular vesicles can trigger a receptor–ligand signalling pathway or deliver their contents by endocytosis. There are several excellent reviews on extracellular vesicles and their role in modulation of the immune system[73,74]. For this Review, we focus on the interaction of extracellular vesicles with the immune system in the context of obesity (Fig. 2).

Obesity, extracellular vesicles and immune modulation. Adipose tissue is a major source of circulating extracellular vesicles. Compared with people without obesity, people with obesity generally have higher levels of extracellular vesicles in their serum[75,76]. The cause of this increase is not known, although it has been suggested that adipose tissue in the obese state might have a higher rate of extracellular vesicle production and/or there might be decreased clearance of extracellular vesicles by the liver[77]. Of note, bariatric surgery or caloric restriction reduces the number of circulating extracellular vesicles, suggesting that a reduction in adipose tissue mass results in the decreased secretion of extracellular vesicles[76,78].

Extracellular vesicles from animals or humans with obesity are also phenotypically different from those generated in a lean state. Notably, extracellular vesicles from obese mice induced glucose intolerance and insulin resistance when injected into lean mice, purportedly owing to the activation of adipose tissue macrophages, which are associated with increased insulin resistance[79]. Several studies report that extracellular vesicles released from adipocytes in the obese state contain factors that alter systemic metabolism[80,81]. For example, an increase in the levels of specific exosomal microRNAs (miRNAs) that are associated with glucose intolerance was reported in obese mice compared with lean mice[82]. In addition, pro-inflammatory M1-like polarization was reported to be driven by increased numbers of adipocyte-derived extracellular vesicles carrying the signalling protein Sonic hedgehog in cultured macrophages from individuals with type 2 diabetes mellitus, which could thereby contribute to insulin resistance[83]. Other studies have also linked adipocyte-derived extracellular vesicles with decreasing insulin sensitivity through their ability to decrease the expression of insulin receptor substrate 1 (IRS1) and the glucose transporter GLUT4 in skeletal muscle (reviewed in ref. 84).

It is important to note that extracellular vesicles can also be released from different immune cell populations. For example, an early study found that extracellular vesicles released from B cells contained major histocompatibility complex (MHC) class II molecules and could stimulate the secretion of IL-2 by T cell hybridoma cells[85]. Additional papers have described the crucial function of extracellular vesicles in immunoregulation, including antigen presentation[86], immune activation[87,88], immunosuppression[88,89] and wound healing[90]. However, how obesity influences the immunomodulatory effects of extracellular vesicles has not been extensively studied.

Various animal models and human studies have been used to investigate the effects of obesity on extracellular vesicle function in an immune context. Extracellular vesicles derived from macrophages and dendritic cells contain IL-1β, a pro-inflammatory cytokine, as well as enzymes that synthesize pro-inflammatory leukotrienes, such as leukotriene B4 (LTB4) and leukotriene C4 (LTC4)[81,91]. Given this

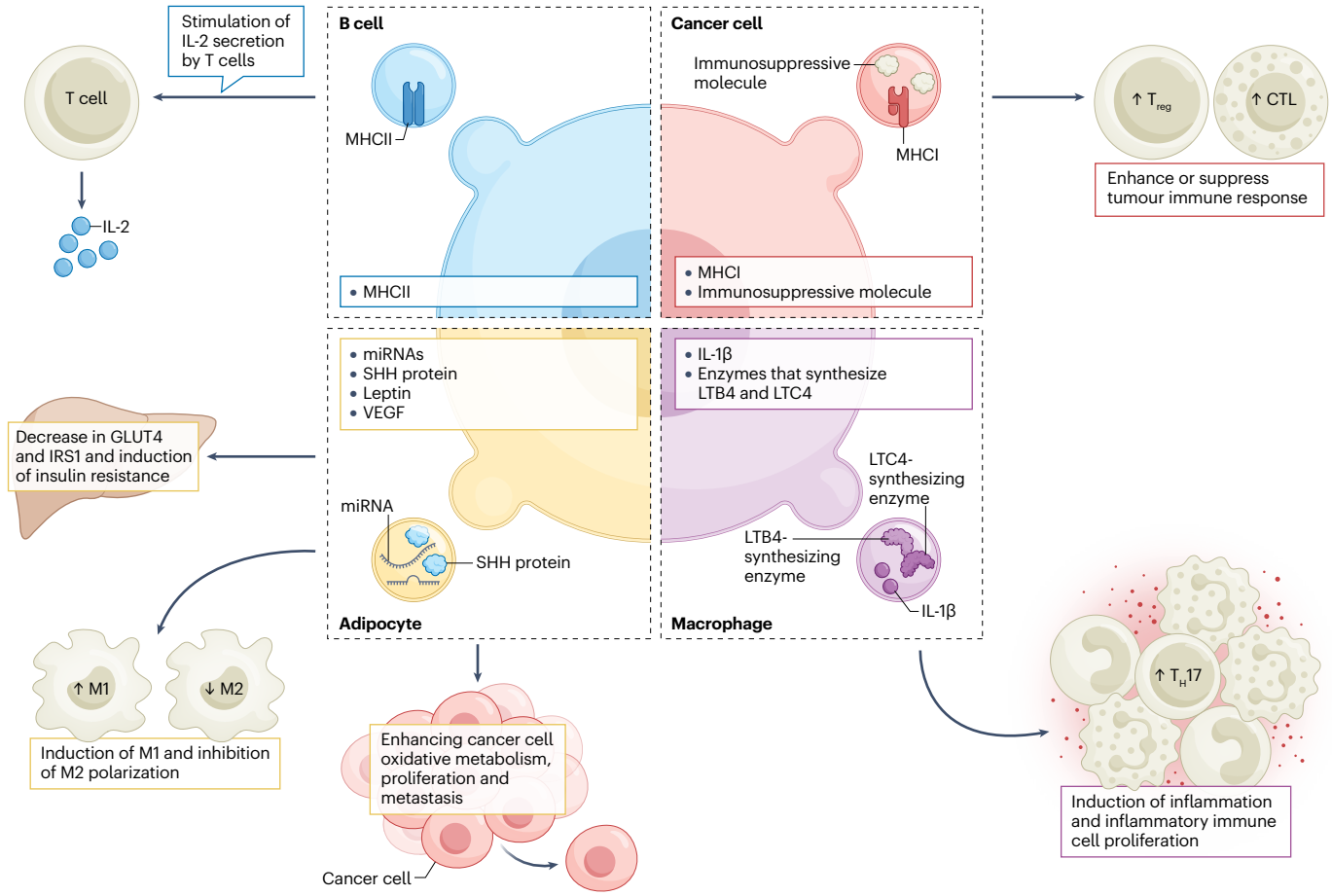

Fig. 2 | Extracellular vesicles and their effect on immune functions. Several types of cell can produce extracellular vesicles, including adipocytes, immune cells and cancer cells. Depending on their cargo, these extracellular vesicles have different effects on target cells. Extracellular vesicles carrying different cargoes can influence various processes, such as T cell IL-2 secretion, insulin resistance, cancer cell oxidative metabolism and polarization of immune cell populations. CTL, cytotoxic T lymphocyte; IRS, insulin receptor substrate; LTB4, leukotriene B4; LTC4, leukotriene C4; M1, M1-like macrophage; M2, M2-like macrophage; MHCI, major histocompatibility complex class I; MHCII, major histocompatibility complex class II; miRNA, microRNA; T_H17, T helper 17 cell; T_{reg}, regulatory T cell; SHH, Sonic hedgehog; VEGF, vascular endothelial growth factor.

observation, it is intriguing to speculate that obesity might drive higher levels of extracellular vesicles containing pro-inflammatory cytokines and leukotrienes that would promote systemic and tissue-specific inflammation. Notably, adipocytes from obese animals secrete exosomes (a subpopulation of extracellular vesicles) containing higher levels of a specific miRNA (miR-34) that inhibits M2 polarization, thus dampening an anti-inflammatory phenotype, compared with lean mice[92]. Furthermore, deletion of miR-34 in obese mice improved glucose tolerance, decreased insulin resistance and reduced systemic inflammation. Adipose tissue constitutes a major source of exosomal miRNAs in the circulation and, during obesity, the levels of another miRNA, miR-155 (which modulates macrophage polarization) in exosomes secreted by adipose tissue macrophages increase relative to the levels in lean animals[93], whereas the levels of miR-690 (which confers an anti-inflammatory effect) in exosomes secreted by adipose tissue macrophages decreases compared with the lean counterparts[94]. Exosomes also carry protein cargo, including IL-1β, IL-18, IL-6 and IL-10 (ref. 88), which could potentially influence various immunological outcomes, such as inhibition of dendritic cell maturation and lower T cell proliferation[89].

Extracellular vesicles are also involved in viral infection[95]. For example, extracellular vesicles transport viral components, thereby facilitating the spread of virus to uninfected cells. In addition, during infection, extracellular vesicles can transport proteins, mRNA, miRNA and other mediators that can influence the cellular response by priming cells either to activate antiviral defence mechanisms or for further viral infection. However, less is known about how extracellular vesicles function in a host with obesity with respect to the response to infection. As noted earlier, obesity is associated with an increase in the number of adipose-derived extracellular vesicles, and these extracellular vesicles tend to be pro-inflammatory. This pro-inflammatory status could affect the ability of the immune cells to respond appropriately to infection in the obese state. Of particular note, adults with obesity are more likely than those without obesity to have a severe outcome from infection with influenza virus or SARS-CoV-2, which could be attributed to obesity-induced chronic inflammation[96]. Although it is clear that

obesity can alter the metabolism of adaptive immune cells, the role of extracellular vesicles in this alteration remains to be elucidated.

Extracellular vesicles and cancer. Extracellular vesicles are also associated with cancer and have been reported to both promote and suppress tumours. Extracellular vesicles derived from adipose tissue that surrounds breast cancer (cancer-associated adipocytes, CAAs) contain leptin, vascular endothelial growth factor and miRNAs, among other factors, which can promote the spread of the cancer[97]. The increase in adipose tissue associated with obesity is thought to contribute to the increased risk of specific types of cancer, including breast cancer, owing, in part, to an increase in CAA-derived vesicles. These CAA-derived extracellular vesicles also influence tumour metabolic processes, transferring fatty acid substrates and proteins involved in fatty acid oxidation, mitochondrial respiration and ATP production, and these tumour-promoting extracellular vesicle activities are enhanced in the presence of obesity[98].

Conversely, extracellular vesicles from cancer cells can deliver tumour-associated antigens, peptide–MHC complexes and immune stimulatory factors to dendritic cells to enhance the immune response to the cancer[99]. However, extracellular vesicles from cancer cells have also been reported to carry immunosuppressive factors, thereby dampening the immune response to the tumour[100]. Extracellular vesicles are actively being studied for their potential use as cancer therapeutics as well as for diagnostic biomarkers for cancer progression.

Box 2

Oxylipins derived from polyunsaturated fatty acids

Oxylipins are enzymatic and non-enzymatic derivatives of monounsaturated fatty acids and polyunsaturated fatty acids (PUFAs). Eicosanoids are oxylipins that are generally synthesized from 20-carbon long-chain PUFAs. Eicosanoids are synthesized in response to the enzyme-mediated cleavage of PUFAs from membrane phospholipids, which involves the binding of PUFAs to various enzymes, such as lipoxygenases and cyclooxygenases. Classic eicosanoids generated from the *n*-6 PUFA arachidonic acid have roles in promoting inflammation. Eicosanoids can also be generated from *n*-3 PUFAs, such as eicosapentaenoic acid (EPA); EPA-derived prostaglandin E_3, for example, has anti-inflammatory properties. Monohydroxy oxylipins from *n*-3 PUFAs, such as 14-hydroxyeicosapentaenoic acid (14-HDHA), 17-HDHA and 18-hydroxyeicosapentaenoic acid (18-HEPE), have a role in various immunological processes. However, there is a wide range of other monohydroxylated PUFAs that might also target innate and adaptive immunity, which remain to be studied. The monohydroxylated derivates of oxylipins are also precursors for specialized pro-resolving mediators (SPMs), which exert their effects by targeting different G protein-coupled receptors to activate the resolution phase of inflammation. There is emerging evidence that exogenous administration of monohydroxylated derivates of PUFAs and their downstream metabolites can trigger pathways of inflammation resolution.

Extracellular vesicles and autoimmunity. Little is known about the role of obesity-associated extracellular vesicles in autoimmune diseases. Obesity is associated with several autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease and psoriasis, yet it is not clear how obesity-associated extracellular vesicles might contribute to these diseases. Extracellular vesicles have been reported to contain pro-inflammatory and anti-inflammatory mediators, including specific miRNAs, in rheumatoid arthritis models and patient samples[101].

Oxylipins

Excess nutrient intake contributes to chronic inflammation, which is central to the pathophysiology of obesity[5]. Various metabolic tissues, such as the liver, skeletal muscle, brain, white adipose tissue and pancreas, become inflamed as adiposity increases. As reviewed by others, expansion of white adipose tissue leads to enrichment, and changes in the activity, of immune cell populations such as M1-like macrophages, $CD19^+$ B cells and pro-inflammatory $CD4^+$ and $CD8^+$ T cell subsets[102]. Furthermore, expansion of adipose tissue leads to secretion of pro-inflammatory cytokines and oxidative stress. Ultimately, these changes culminate in an inflamed microenvironment. At a molecular level, inflammation is controlled by the metabolism of PUFAs. Notably, PUFAs (and, occasionally, mono-unsaturated fatty acids) give rise to oxidized lipids, called oxylipins (Box 2), that control inflammation.

Obesity and *n*-6 PUFA-derived oxylipins. Classically, eicosanoids, such as prostaglandins, derived from *n*-6 PUFAs (Fig. 3), are pro-inflammatory oxylipins; they initiate different inflammatory circuits that control aspects of physiology, including immune cell recruitment at sites of injury, vasodilation and blood clotting. These pathways are established targets for therapies such as NSAIDs, which prevent the generation of *n*-6 PUFA-derived eicosanoids and thereby suppress the cardinal signs of inflammation. As an example, LTB4 generated from the *n*-6 PUFA arachidonic acid is a chemoattractant for select macrophage populations in white adipose tissue, liver and skeletal muscle[103]. Inhibition of the LTB4 receptor in obese mice reduces peritoneal macrophage chemotaxis to target organs and improves the tissue inflammatory profile, glucose and insulin homeostasis and hepatic steatosis[103]. By contrast, excess LTB4 production leads to increased chemotaxis of circulating B cells into white adipose tissue, which drives inflammation, contributes to insulin resistance and might even induce the production of autoimmune antibodies[103,104].

There is an increasing appreciation that brain inflammation could contribute to alterations in feeding behaviours that are associated with obesity, specifically by increasing food intake. Levels of the eicosanoid prostaglandin E_2 (PGE_2), synthesized from arachidonic acid, were shown to be increased in the hypothalamus of mice fed a high-fat diet relative to control mice, and genetic inhibition of the PGE_2 receptor in microglial cells led to a decrease in food intake, resulting in a decrease in weight and improved insulin sensitivity[105]. This result underscores how activation of the PGE_2 receptor in microglial cells might be crucial in mediating inflammatory signalling and dysregulated food intake in the brain. Increased pulmonary inflammation in response to obesity is also an area for study, in conjunction with air pollutants or pulmonary infections. One study reported that levels of cyclooxygenase-2-derived oxylipins increased in the lungs of obese mice before infection, and another study showed that the levels of nearly all major oxylipins were elevated with murine obesity before and after acute exposure to ozone[106,107]. There is also compelling evidence that air pollutants such

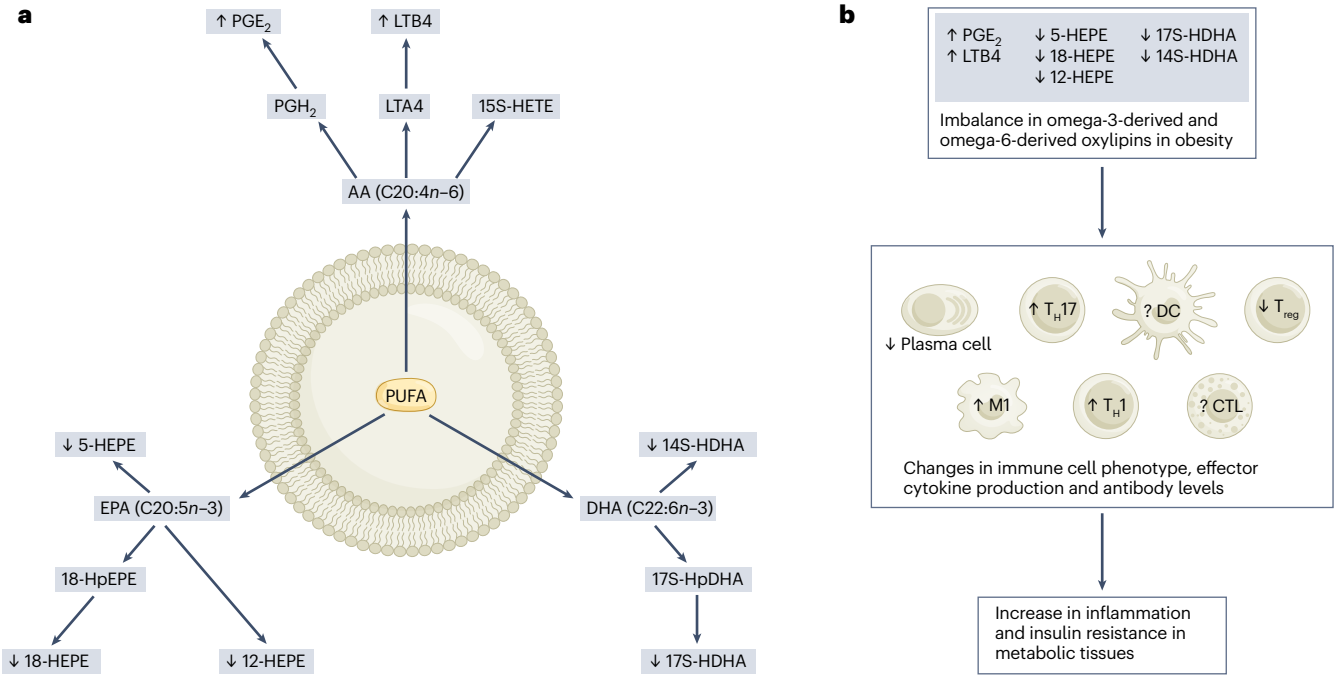

Fig. 3 | Molecular pathways by which select monohydroxy oxylipins synthesized from polyunsaturated fatty acids control immunological responses in obesity. a, Long-chain polyunsaturated fatty acids (PUFAs) are substrates for enzymes that generate downstream oxylipins. Arachidonic acid (AA), an *n*-6 PUFA, gives rise to a wide range of downstream metabolites; notably, leukotriene B4 (LTB4), which is increased in response to increased adiposity and drives a pro-inflammatory response in various tissues. Different oxylipins are also generated from the long-chain *n*-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). **b**, These oxylipins have a wide range of roles in controlling innate and adaptive immunity. For simplicity, other oxylipins, including those generated from non-enzymatic pathways or those of the specialized pro-resolving mediator (SPM) family, are not shown. CTL, cytotoxic T lymphocyte; DC, dendritic cell; HDHA, hydroxydocosahexaenoic acid; HEPE, hydroxyeicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; LT, leukotriene; M1, M1-like macrophage; PG, prostaglandin; T_H1, T helper 1 cell; T_H17, T helper 17 cell; T_{reg}, regulatory T cell.

as ozone augment the effects of obesity through an increase in levels of pulmonary IL-33; however, the role of inflammatory oxylipins in this process remains to be investigated[108].

Obesity and *n*-3 PUFA-derived oxylipins. A wide range of oxylipins that might have a role in controlling differing aspects of immunity can be generated from long-chain *n*-3 PUFAs. There is evidence of an imbalance in the production of oxylipins synthesized from the *n*-3 PUFA docosahexaenoic acid (DHA) in humans and mice with obesity[109–113]. For instance, levels of the monohydroxy enzymatic derivates of DHA, 14-hydroxydocosahexaenoic acid (14-HDHA) and 17-hydroxydocosahexaenoic acid (17-HDHA), are decreased in plasma, serum and leukocytes of individuals with obesity compared with individuals without obesity[111]. These oxylipins in mice or in culture boost humoral immunity by promoting the differentiation of B cells to antibody-secreting $CD138^+$ plasma cells[114]; 14-HDHA and 17-HDHA are robustly detectable and are likely to have many immunological roles that remain to be established[115]. The cellular targets of 14-HDHA and 17-HDHA in obesity remain to be investigated. Interestingly, a rodent study of pulmonary hypertension showed that 14-HDHA and 17-HDHA were produced by eosinophils; when secreted, these oxylipins exerted anti-inflammatory effects by inhibiting neutrophil, monocyte and macrophage recruitment in a manner that was dependent on the G protein-coupled receptor *N*-formyl peptide receptor 2 (FPR2)[116]. These results raise the possibility that increasing the levels of 14-HDHA and 17-HDHA could have potential benefits for certain pulmonary infections in individuals with obesity.

Levels of other DHA-derived oxylipins, such as those of the specialized pro-resolving mediator (SPM) family-like maresins[117], are also decreased in individuals with type 2 diabetes mellitus, a major comorbidity of obesity[118]. Interestingly, cold exposure or β3-adrenergic stimulation increases the biosynthesis of the SPM maresin 2 in brown adipose tissue, which, in turn, lowers circulating levels of tumour necrosis factor and decreases hepatic inflammasome gene expression while increasing the levels of hepatic $CCR2^+Ly6C^{hi}$ monocytes that express the anti-inflammatory protein TREM2 (ref. 119). SPMs have a strong therapeutic potential as pharmacological agents to lower inflammation[115]. However, some research groups have challenged the existence of endogenous SPMs as mediators of inflammation resolution owing to limitations in detecting these oxylipins using mass spectrometry[115,120].

The mechanisms by which obesity lowers the levels of DHA-derived oxylipins remain to be established. Experiments using cultured leukocytes isolated from individuals with morbid obesity suggest that the activities of 15-lipoxygenase and 5-lipoxygenase, which are required for the synthesis of oxylipins downstream of DHA, are impaired[111]. Interestingly, the reduction in the levels of 14-HDHA and 17-HDHA seen in individuals with obesity is not caused by a decrease in circulating levels of DHA, and short-term weight loss after bariatric surgery does not restore levels of these oxylipins[112]. Furthermore, administration of

n-3 PUFA-enriched marine oils does not appear to robustly increase the levels of DHA-derived oxylipins in individuals with obesity[113,121]. Indeed, a randomized clinical trial showed that marine oil supplementation robustly increased the levels of monohydroxy oxylipins in subcutaneous white adipose tissue of lean individuals but not in individuals with obesity[113]. These findings suggest that the direct administration of oxylipins to individuals with obesity might be required, as the enzymes for synthesizing oxylipins from *n*-3 PUFAs are probably not efficient.

There is also evidence that obesity dysregulates the abundance of oxylipins synthesized from another long-chain *n*-3 PUFA, eicosapentaenoic acid (EPA). As one example, levels of the oxylipin 12-hydroxyeicosapentaenoic acid (12-HEPE) synthesized from EPA via 12-lipoxygenase are decreased in individuals with obesity compared with controls. Furthermore, levels of 12-HEPE (in addition to 14-HDHA levels) correlate negatively with insulin resistance[122]. Experiments in mouse models show that 12-HEPE is a batokine (a factor derived from brown adipose tissue) that improves glucose uptake into adipocyte and skeletal muscle[122]. Studies have also revealed a decrease in 12-HEPE and 18-HEPE levels in mice fed a high-fat diet relative to lean controls[123]. A key question, however, is what are the cellular targets of metabolites such as 12-HEPE and 18-HEPE? Evidence from studies in mice suggest that 18-HEPE can inhibit pro-inflammatory responses from macrophages[124,125]. Furthermore, 18-HEPE might confer its effects through its downstream metabolites (E-series resolvins, which are SPMs), which control inflammatory responses by inhibiting LTB4 signalling via neutrophils, monocytes and macrophages[126]; therefore, decreased levels of 18-HEPE in obesity would be expected to compromise these effects.

Many other *n*-3 PUFA-derived oxylipins, particularly monohydroxy derivatives, might also confer an anti-inflammatory role that becomes compromised in obesity[126]. For instance, 5-HEPE promotes the induction of T_{reg} cells in vitro, although the implication of this finding in vivo with obesity is unknown[127]. Furthermore, administration of 8-HEPE to

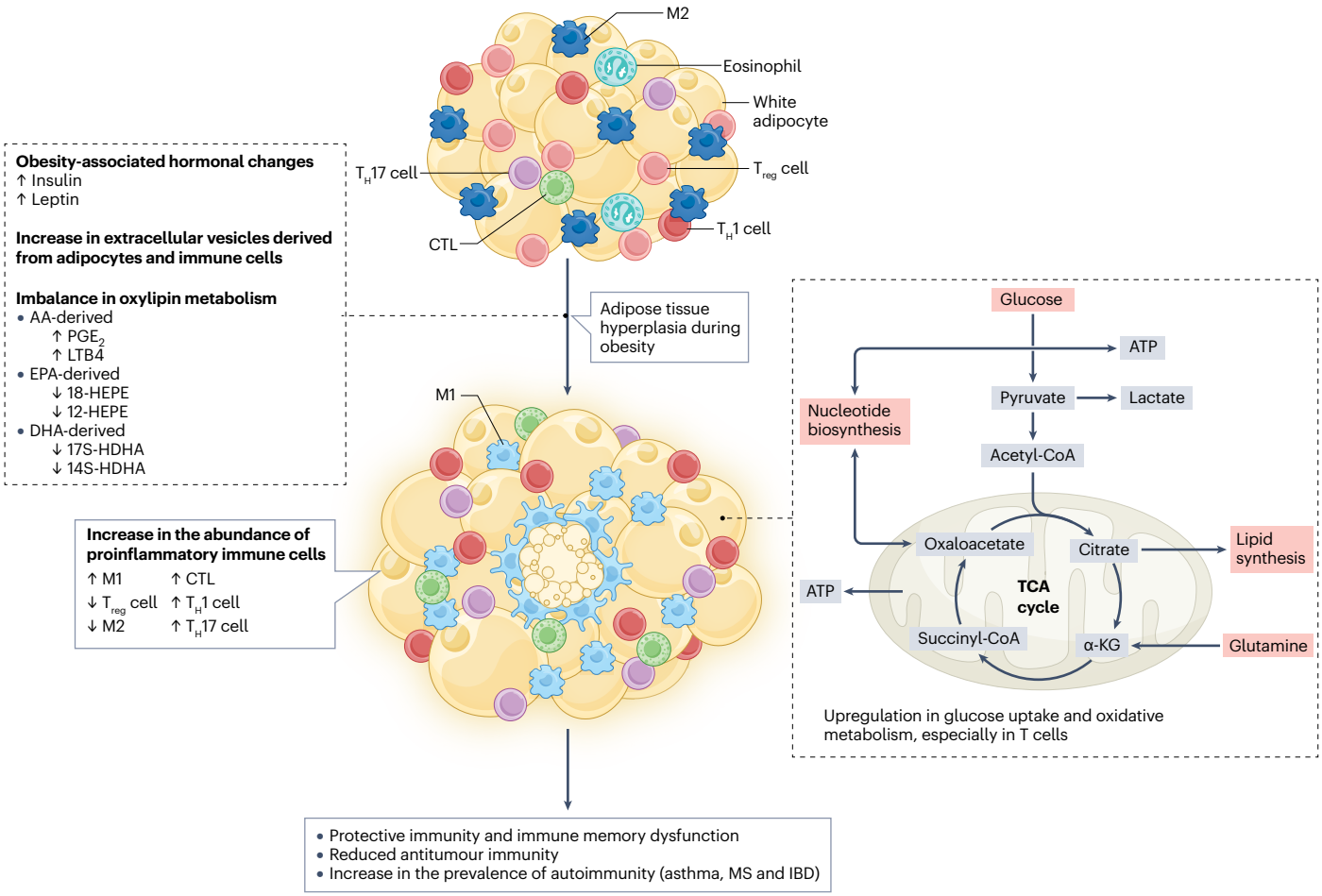

Fig. 4 | Proposed mechanisms leading to obesity-associated immune dysfunction. In obesity, the expansion of adipose tissue leads to an increase in the secretion of leptin and insulin and of adipocyte-derived extracellular vesicles carrying immunomodulating cargo. In addition, obesity drives a shift towards the synthesis of *n*-6 polyunsaturated fatty acid (PUFA)-derived oxylipins. These obesity-driven changes lead to an increase in pro-inflammatory immune cells with altered metabolism, resulting in increased inflammation and autoimmunity, as well as decreased protective immunity against pathogens and unchecked tumour growth. α-KG, α-ketoglutarate; AA, arachidonic acid; CTL, cytotoxic T lymphocyte; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDHA, hydroxydocosahexaenoic acid; HEPE, hydroxyeicosapentaenoic acid; IBD, inflammatory bowel disease; LTB4, leukotriene B4; M1, M1-like macrophage; M2, M2-like macrophage; MS, multiple sclerosis; PG, prostaglandin; TCA cycle, tricarboxylic acid cycle; T_H1 cell, T helper 1 cell; T_H17 cell, T helper 17 cell; T_{reg} cell, regulatory T cell.

obese mice lowers hepatic and circulating levels of triglycerides by inducing the activation of PPARα, which controls lipid biosynthesis, β-oxidation and inflammation. However, the cellular target of 8-HEPE remains to be established[128]. Other DHA-derived oxylipins, such as 7-HDHA, which has been identified as a PPARα ligand, should also be studied[129]. Finally, it will be interesting to determine whether extracellular vesicles are enriched in different *n*-3 PUFA-derived oxylipins, as well as the potential impact of these *n*-3 PUFA-containing extracellular vesicles on inflammatory cell signalling.

It is important to acknowledge that a wide range of other oxylipins are also generated from EPA and DHA through a series of biochemical pathways, although an overview of these additional oxylipins is beyond the scope of this Review[130]. For instance, EPA and DHA are precursors of endocannabinoids, which have a wide range of signalling roles in physiology, including control of inflammation[131]. Interestingly, EPA-derived and DHA-derived endocannabinoids can be metabolized by cyclooxygenases, lipoxygenases and CYP450s to generate downstream oxylipins that are hypothesized to have roles that include lowering the levels of inflammatory cytokines and *n*-6 PUFA-derived pro-inflammatory oxylipins, such as prostaglandins[129].

A key area for future investigation is the identification of the cellular targets of oxylipins, particularly those derived from *n*-3 PUFAs that are abundant in mice and humans. There is strong evidence that EPA and DHA can exert immunomodulatory effects in various tissues and cell types by blocking the maturation of human monocyte-derived dendritic cells and the formation of different $CD4^+$ T cell subsets including pro-inflammatory T_H1 or T_H17 cells[113,132–134]. The underlying mechanisms of PUFAs in this context involve not just the production of oxylipins but also targeting of the biophysical organization of lymphocyte and mast cell lipid rafts to decrease downstream signalling and inflammatory gene expression[135–137].

Heterogeneous immune responses

Owing to its multifactorial aetiology, obesity is not a single disease state, and therefore therapeutics to target mechanisms related to immunity will need to account for heterogeneity in individuals with obesity[4]. There are many sources of heterogeneity, including sex, age of onset of obesity, race and ethnicity, microbiome composition and diversity, the perception of taste and palatability of foods, and genetics. Heterogeneity also exists at the tissue and cellular levels, as is evident from the differing depots of adipose tissue and the vastly differing cell types found within a given metabolic or immunological tissue.

As one example of heterogeneity, there are strong differences between male and female mice in their response to a high-fat diet. Female mice are protected from high-fat diet-induced metabolic impairments compared with male mice of the same age and fed the same high-fat diets; this protection might be the consequence of an increase in the number of adipose tissue T_{reg} cells, which increase in abundance in females but decrease in males fed a high-fat diet over the course of 14 weeks[138]. Similarly, there are several studies that demonstrate that the levels of inflammatory oxylipins differ between human male and female individuals. Premenopausal female individuals were shown to have higher levels of plasma oxylipins synthesized from 12-lipoxygenase, such as 14-HDHA and 12-HEPE, compared with older female and male individuals[139]. In addition, ovariectomy in mice increases pulmonary inflammation in response to an air pollutant and decreases the levels of pulmonary DHA-derived oxylipins, suggesting a potential role for sex hormones in the regulation of oxylipin production[140].

Compelling studies also show that the generation of different oxylipins might be dependent on host genetics. For instance, several polymorphisms in CYP450 enzymes, which metabolize PUFAs, have been identified in individuals with type 2 diabetes mellitus, and some of these polymorphisms might be relevant for drug interventions in select clinical populations[141].

Overall, there is a need to account for heterogeneity in the human population at a basic level. The use of population-based approaches, such as Collaborative Cross and Diversity Outbred mice, can facilitate a better understanding of how obesity influences mechanisms related to innate and adaptive immunity. The advantage of these models, particularly Diversity Outbred mice, is that they are effective tools to model human genetic diversity, which is difficult to achieve with inbred mouse models[142]. In addition, clustering of large datasets on the basis of metabolic, genetic and immunological pathways or biomarkers of disease will enable the efficacy of interventions that target specific molecular pathways to be further refined. Systems approaches will be particularly useful for guiding precision nutrition and medicine-based interventions to target the link between obesity and impaired immunity[143].

Conclusions

Various aspects of immunity are dysregulated in obesity through several overlapping mechanisms, which impact the response to infection, glucose homeostasis, autoimmunity and tumour surveillance (Fig. 4). Key emerging mechanisms in response to increased adiposity include hormonal changes that have direct consequences for immunometabolism and inflammation, modification of the abundance and composition of extracellular vesicles that control immune activation and suppression as well as systemic metabolism, and impairments in the biosynthesis of oxylipins that are crucial for the control of inflammation. To advance the field, there remains a need to further investigate these emerging mechanisms by which immunity is impaired in obesity. For example, what are the key pathways downstream of hormone signalling that can be targeted to improve immune cell metabolism and function in obesity? What are the mechanisms that mediate the effects of obesity and/or obesity-induced inflammation on the biogenesis, release and function of extracellular vesicles? Moreover, what are the cellular targets and molecular mechanisms by which oxidized derivates of PUFAs and their parent molecules control immunity, and how do they control the inflammatory and metabolic response in obesity? Additional studies to address these questions will need to account for the highly heterogeneous nature of obesity in the human population.

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M.A.B., S.R.S. and N.J.M. researched data for the article, contributed substantially to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission. Y.A. contributed substantially to discussion of the content and wrote the article.

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S.R.S. has received industry support from Wiley Companies and Metagenics for studies on *n*-3 and *n*-7 fatty acids and from Sanofi, Solutex and Wiley Companies for organizing conferences. N.J.M., Y.A. and M.A.B. declare no competing interests.

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