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REVIEW

The cellular and signaling networks linking the immune system and metabolism in disease

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It is now recognized that obesity is driving the type 2 diabetes epidemic in Western countries. Obesity-associated chronic tissue inflammation is a key contributing factor to type 2 diabetes and cardiovascular disease, and a number of studies have clearly demonstrated that the immune system and metabolism are highly integrated. Recent advances in deciphering the various cellular and signaling networks that participate in linking the immune and metabolic systems together have contributed to understanding of the pathogenesis of metabolic diseases and may also inform new therapeutic strategies based on immunomodulation. Here we discuss how these various networks underlie the etiology of the inflammatory component of insulin resistance, with a particular focus on the central roles of macrophages in adipose tissue and liver.

The importance of obesity-associated inflammation in disease

Insulin resistance is a characteristic, pathophysiological defect in the majority of individuals with type 2 diabetes mellitus[1,2]. Obesity is the most common cause of insulin resistance, and the current obesity epidemic in the United States and other Western countries is driving a parallel type 2 diabetes epidemic[1,3,4]. These epidemics represent one of the greatest threats to global human health. The abnormalities associated with obesity also increase susceptibility to other diseases, such as cardiovascular disease, stroke and cancer. In 2007, the annual health spending in the United States attributable to diabetes was $174 billion[5], and these costs are projected to continue rising dramatically. There is a huge and unmet need for effective treatment of these metabolic disorders; therefore, it is crucial to understand the mechanisms underlying type 2 diabetes and other metabolic diseases. In this review, we focus on the field of immunometabolism, which has provided promising insights into the pathogenesis of metabolic diseases and also has the potential to provide new therapies for these conditions.

Obesity-associated tissue inflammation is now recognized as a major cause of decreased insulin sensitivity[6–9]. Although a connection between inflammation and diabetes was suggested more than a century ago[10], the evidence that inflammation is an important mediator in the development of insulin resistance came about fairly recently. Approximately 20 years ago, Feingold and Grunfeld observed that administration of the proinflammatory cytokine tumor necrosis factor-α (TNF-α) led to increased serum glucose concentrations, which prompted them to suggest that hyperglycemia may be exacerbated by cytokine overproduction[11,12]. However, the first studies that established the concept of obesity-induced adipose tissue inflammation were conducted by Hotamisligil *et al.*[13], who found that TNF-α was elevated in obese rodents and that neutralization of TNF-α ameliorated insulin resistance. Additionally, mice deficient in TNF-α showed improved insulin sensitivity in diet-induced obesity[14]. A mechanistic link between inflammatory processes and insulin resistance was further established by showing that the signaling pathways leading to activation of inhibitor of κB kinase-β (IKK-β) and nuclear factor-κB (NF-κB) are stimulated in obesity and insulin resistance[15,16]. Yin *et al.*[15] found that TNF-α–mediated activation of IKK *in vitro* could be blocked by the administration of salicylates, which indicated that the anti-inflammatory properties of salicylates are mediated, in part, by the inhibition of IKK-β. Yuan *et al.* showed that heterozygous deletion of IKK-β protected mice from development of insulin resistance during high-fat feeding and that inhibiting these pathways with salicylates attenuated insulin resistance in rodents[16] and in humans[17]. Chronic low-grade inflammation induced by obesity leads to activation of other protein kinases, such as Jun N-terminal kinases (JNKs), and ablation of JNK in mice fed a high-fat diet (HFD) leads to protection from diet-induced obesity and inflammation[18–20]. Activation of inflammatory pathways has since been observed in all classical insulin target tissues, including fat[21,22], liver[23] and muscle[24,25] (**Fig. 1**), indicating that inflammation has a broad role in driving the pathogenesis of systemic insulin resistance.

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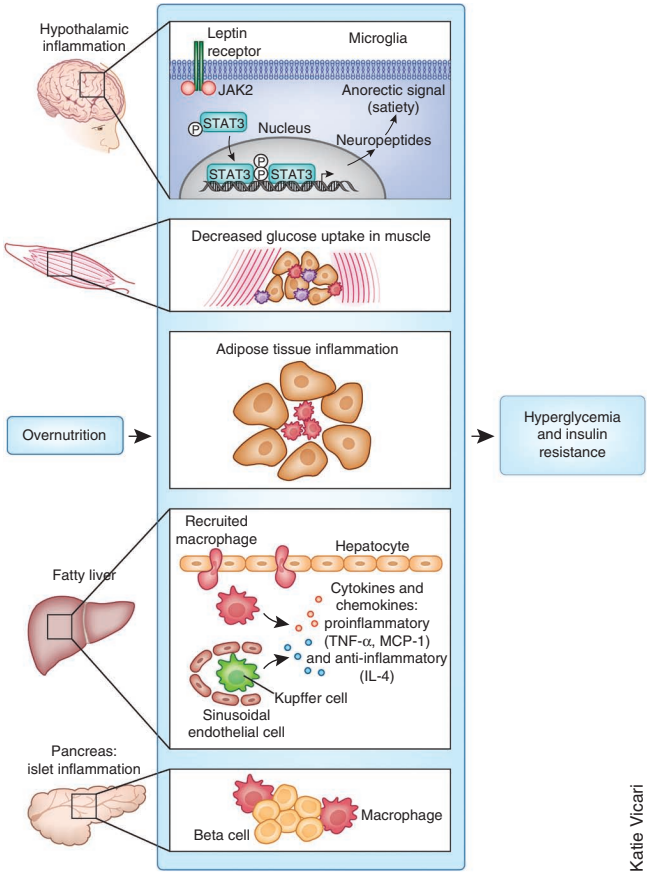

Figure 1 Schematic of integrative physiology. Nutrient overload activates inflammatory responses in adipose tissue, liver, skeletal muscle, pancreas and the hypothalamus, contributing to systemic insulin resistance and glucose intolerance. STAT3, signal transducer and activator of transcription-3; JAK2, Janus kinase-2.

Macrophages have a central role in obesity-associated inflammation

Macrophages infiltrate adipose tissue. An important finding that helped elucidate the cause of tissue inflammation was that adipose tissue from obese mice and humans is infiltrated with large numbers of macrophages[21,22] (**Fig. 2**). These adipose tissue macrophages (ATMs) can comprise up to 40% of the cells in obese adipose tissue[22]. ATMs and adipose tissue inflammation have been extensively studied, and ATMs have been shown to have a key role in systemic insulin resistance, glucose tolerance and the development of metabolic syndrome and type 2 diabetes[26]. In obesity, the proinflammatory pathways in ATMs are highly activated, leading to the secretion of a variety of cytokines, such as TNF-α and interleukin-1β (IL-1β)[26]. These cytokines can act locally in a paracrine manner, or they can leak out of the adipose tissue, which might have systemic effects (endocrine actions), causing decreased insulin sensitivity in insulin target cells (adipocytes, hepatocytes and myocytes).

Adipose tissue not only acts as a storage depot for excess calories but also makes fatty acids and adipokines that can have systemic effects. Clearly, inflammation in adipose tissue could modulate the composition of secreted factors. Furthermore, all adipose tissue is not created equal: visceral adipose tissue exerts greater adverse metabolic effects than subcutaneous fat on insulin sensitivity[27], and some reports have suggested that subcutaneous fat may actually be beneficial[28]. Compared with subcutaneous fat, visceral adipose accumulates more inflammatory ATMs in obesity and secretes greater amounts of proinflammatory cytokines, which may partly explain why visceral adipose tissue is metabolically more harmful than subcutaneous fat[29]. However, it remains to be determined whether subcutaneous fat is the source of secreted factors that promote insulin sensitivity. Another difference between visceral and subcutaneous fat is that the free fatty acids (FFAs) produced from lipolysis of visceral adipose travel directly to the liver via the hepatic blood supply, whereas FFAs from subcutaneous fat enter peripheral circulation. Nielsen *et al.*[30] showed that the contribution of visceral adipose tissue to hepatic FFA delivery increases with increasing visceral fat in humans; therefore, increases in visceral adipose tissue could be an important contributing factor in development of hepatic insulin resistance.

Recruiting macrophages to adipose tissue. The recruitment of macrophages into adipose tissue is the initial event in obesity-induced inflammation and insulin resistance. As a general model, overnutrition causes adipocytes to secrete chemokines such as monocyte chemotactic protein-1 (MCP-1), leukotriene B4 (LTB4) and others, providing a chemotactic gradient that attracts monocytes into the adipose tissue, where they become ATMs (**Fig. 2**). Once proinflammatory ATMs migrate into adipose tissue, they also secrete their own chemokines, attracting additional macrophages and setting up a feed-forward inflammatory process[26].

MCP-1 is an important chemokine that is secreted by enlarging adipocytes[31] and binds to the chemokine (C-C motif) receptor 2 (CCR2) on macrophages to stimulate macrophage migration[32,33]. Deletion of macrophage CCR2 or adipose-tissue MCP-1 can lead to a decrease in ATM content in obesity, reduce tissue markers of inflammation and ameliorate insulin resistance[34]. However, not all studies agree[35] on the roles of CCR2 and MCP-1 in macrophage recruitment, and this issue remains to be fully resolved.

Several other chemokines have been implicated in the recruitment of inflammatory cells. LTB4 was discovered on the basis of its potent chemotactic activity on neutrophils[36] and, as a product of arachidonic acid metabolism, it is produced by adipocytes[37], where it can contribute to ATM infiltration. Indeed, recent studies have shown that knocking out the gene encoding the LTB4 receptor BLT1 can protect mice from obesity-induced inflammation and insulin resistance[38]. Fractalkine (CX3CL1) and its receptor CX3CR1 have been implicated in the recruitment and adhesion of both monocytes and T cells in atherosclerosis[39]. Fractalkine is expressed in adipocytes[40] and macrophages[41], is markedly upregulated in obese human adipose tissue[42] and contributes to the adhesion of monocytes to adipocytes[43]. The CX3CL1-CX3CR1 system plays an important part in chronic inflammatory diseases such as atherosclerosis[44], but whether it has any role in adipose tissue inflammation is unknown. Although the concentrations of many proinflammatory chemokines are elevated in obese white adipose tissue, not all of them are involved in ATM accumulation[45]. Inhibition of single chemokines can have effects on the chemotaxis of inflammatory cells when they are studied individually *in vitro* or *ex vivo*, but it is likely that chemokines function in a combinatorial manner in the more complex *in vivo* situation. It is possible that this factor could provide an explanation for the conflicting results regarding the roles of CCR2 and MCP-1 in obesity-induced inflammation and insulin resistance.

Macrophage subpopulations. Macrophages can be classified into broad groups on the basis of concepts that were derived from *in vitro* experiments in which bone marrow–derived cells were treated with specific

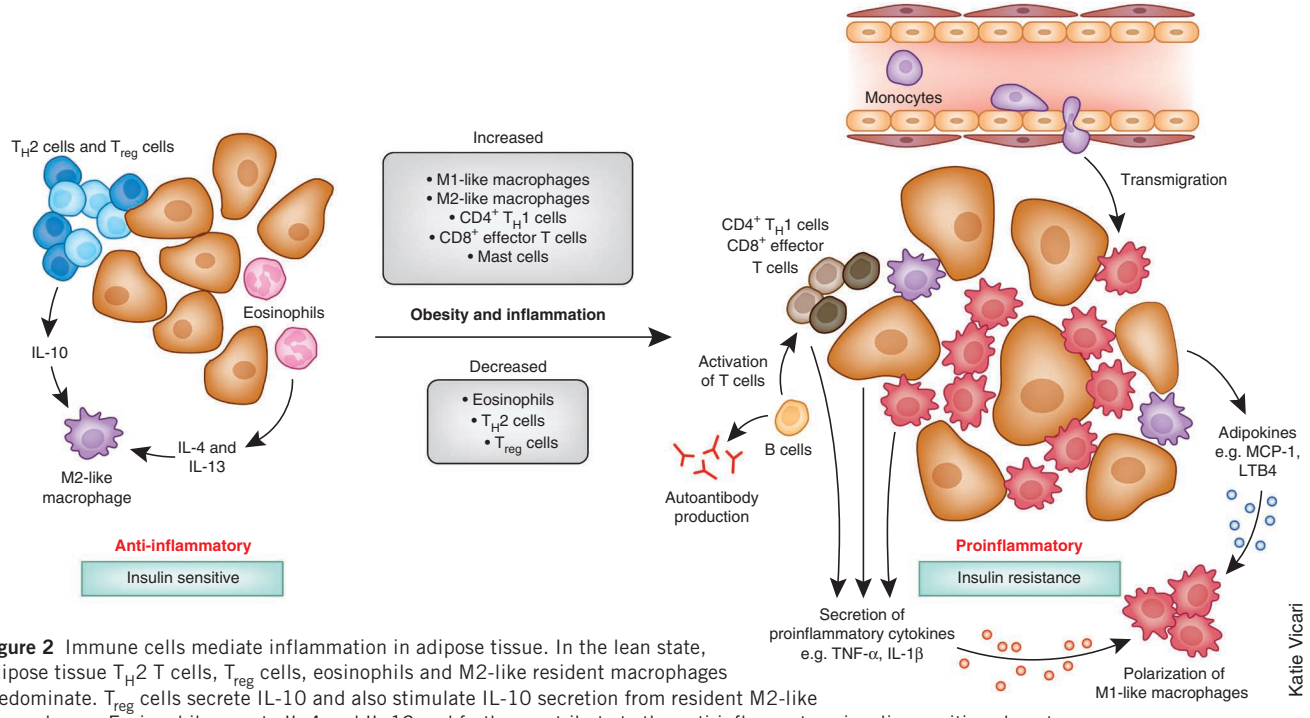

Figure 2 Immune cells mediate inflammation in adipose tissue. In the lean state, adipose tissue T_H2 T cells, T_{reg} cells, eosinophils and M2-like resident macrophages predominate. T_{reg} cells secrete IL-10 and also stimulate IL-10 secretion from resident M2-like macrophages. Eosinophils secrete IL-4 and IL-13 and further contribute to the anti-inflammatory, insulin-sensitive phenotype. In obesity-induced inflammation, immune cells are recruited and contribute to adipose tissue inflammation. Monocytes respond to chemotactic signals and transmigrate into the adipose tissues and become polarized to the highly proinflammatory M1-like state. Once recruited, these M1-like macrophages secrete proinflammatory cytokines that work in a paracrine fashion. The eosinophil content declines in obese adipose tissue. Obesity also induces a shift in adipose tissue T cell populations with a decrease in T_{reg} content and an increase in $CD4^+$ T_H1 and $CD8^+$ effector T cells, which secrete proinflammatory cytokines. B cell numbers also increase and activate T cells, which potentiate M1-like macrophage polarization, inflammation and insulin resistance. Cytokines and chemokines from the adipose tissue can also be released into the circulation and work in an endocrine manner to promote inflammation in other tissues.

growth factors. Classically activated macrophages (CAMs), termed M1, can be induced *in vitro* by growing bone marrow–derived hematopoietic cells with granulocyte-macrophage colony–stimulating factor (GM-CSF). Alternatively activated macrophages (AAMs), termed M2, can be induced by culturing the bone marrow–derived cells with macrophage colony–stimulating factor (M-CSF) and IL-4. M1 macrophages secrete a characteristic signature of proinflammatory cytokines, whereas M2 macrophages secrete anti-inflammatory cytokines (for example, IL-10 and IL-1 receptor antagonist (IL-1Ra))[46].

Tissue macrophages respond to changes in the local environment by changing their polarization status, and, thus, the M1 and M2 classifications are oversimplifications of the more dynamic and varied polarization states of macrophages that can be observed *in vivo*. *In vivo*, it is likely that ATMs span a spectrum, from the M1-like proinflammatory state to the M2-like noninflammatory state. Both M1-like and M2-like populations express F4/80 and CD11b, and the ATM population of M1-like macrophages also expresses $CD11c^{47,48}$. In obesity, $CD11c^+$ ATMs are considered to be M1-like or CAM cell types, whereas the resident macrophages are noninflammatory and $CD11c^-$ and are classified as M2-like or as AAM cell types[47–49]. In the obese state, M1-like ATMs can accumulate lipids, taking on a foamy appearance in the adipose tissue[50]. Increased numbers of M1-like, $CD11c^+$ recruited macrophages account for the majority of the increase in ATMs in obesity[47,48], and >90% of recruited monocytes become $CD11c^+$ ATMs. However, the origin of the resident, M2-like, $CD11c^-$ macrophages is still unclear. It is possible that they either migrate into adipose tissue very infrequently and then proliferate or that they proliferate from a cell type other than circulating monocytes. Indeed, Jenkins *et al.*[51] have recently shown that resident, M2-like AAMs retain a high capacity to proliferate compared with $CD11c^+$ CAMs.

Many studies have confirmed that the polarization state of an ATM correlates well with insulin resistance. For example, Fujisaka *et al.*[52] showed that the number of M1-like ATMs expressing CD11c correlated with insulin sensitivity. Patsouris *et al.*[53] generated transgenic mice expressing the diphtheria toxin receptor driven by the CD11c promoter. When these mice were treated with diphtheria toxin, $CD11c^+$ ATMs were depleted, and this led to reversal of the HFD-induced obese, insulin-resistant, glucose-intolerant state. The phenotype of ATMs is not fixed, and they can repolarize from one state to another. For example, evidence suggests that switching from a HFD to a chow diet[54], or treating obese mice with omega-3 fatty acids[55] or thiazolidinediones (TZDs)[56], can drive conversion from the M1 to the M2 type, coincident with increased insulin sensitivity. In this sense, one can propose that in adipose tissue, the recruited M1-like CAMs are responsible for the inflammatory component of insulin resistance, whereas the resident M2-like AAMs function in remodeling and tissue homeostasis.

Linking macrophage inflammatory signaling to insulin resistance. Several lines of evidence have shown that proinflammatory macrophages can cause insulin resistance, as summarized in **Figure 3**. For example, there are strong correlations between the degree of ATM accumulation and insulin resistance, and macrophages can secrete proinflammatory cytokines, which directly impair insulin action. The most compelling mechanistic evidence has been provided by genetic studies using knockout and transgenic techniques to disarm

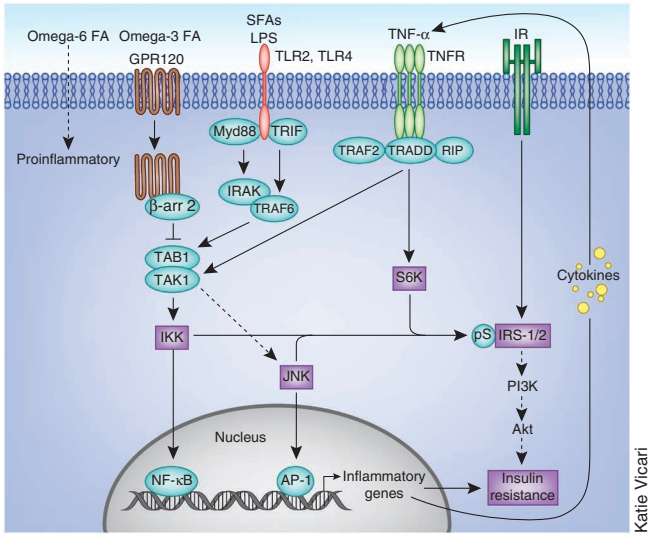

Figure 3 Inflammatory signaling pathways involved in the development of insulin resistance. Stimulation of proinflammatory signaling pathways negatively regulates insulin signaling. Activation of TLR2, TLR4 and/or tumor necrosis factor receptor (TNFR) leads to transforming growth factor-β–activated kinase-1 (TAK1) and TAK1-binding protein-1 (TAB1) association and activation of IKK and JNK, causing serine kinase phosphorylation of IRS-1 or IRS-2 and increased transcription of inflammatory genes, which combine to contribute to insulin resistance. Activation of GPR120 by omega-3 fatty acids (FAs) inhibits TAK activation with subsequent inhibition of inflammatory signaling. Omega-6 FA signaling is proinflammatory. Myd88, myeloid differentiation primary response gene-88; IRAK, interleukin-1 receptor–associated kinase-1; TRAF6, TNF receptor–associated factor-6; β-arr 2, β-arrestin 2; TRADD, TNF receptor–associated death domain; RIP, receptor interacting protein; IR, insulin receptor; PI3K, phosphoinositide 3-kinase; AP-1, activator protein-1; TRIF, TIR domain containing adaptor protein inducing IFN-β.

or disable macrophage-mediated inflammatory pathways (summarized in **Table 1**). For example, deleting IKK-β[57], JNK1 (ref. 20), the insulin receptor[58] or fatty acid–binding protein 4 (FABP4)[59] in macrophages protects mice from obesity-induced insulin resistance. Macrophage-specific deletion of peroxisome proliferator–activated receptor-γ (PPAR-γ), a transcription factor that mediates anti-inflammatory and insulin-sensitizing effects, impairs AAM development, derepresses proinflammatory macrophage pathways and accentuates insulin resistance and glucose intolerance[60,61].

The activation of tissue macrophages triggers the release of cytokines, which can induce insulin resistance in various ways. Among the proinflammatory cytokines, TNF-α is the most studied and has consistently been shown to cause insulin resistance. For example, TNF-α can stimulate serine kinases—including IKK[62], JNK[18], S6 kinase (S6K)[63–65] and mammalian target of rapamycin (mTOR)[64]—which causes serine phosphorylation of insulin receptor substrate-1 (IRS-1), attenuating its ability to propagate downstream insulin signaling. In cultured adipocytes, TNF-α can attenuate insulin signaling by enhancing the expression of suppressor of cytokine signaling (SOCS) proteins that bind the insulin receptor and reduce its ability to phosphorylate IRS proteins[66–68], further strengthening the link between inflammation and insulin resistance.

IL-1β, which is generated by inflammasome activation, can also exert proinflammatory effects[69]. Assembly of the intracellular multimeric inflammasome protein complex in ATMs mediates the cleavage and activation of caspase-1, leading to maturation and release of IL-1β. HFD-induced elevation of fatty acids can activate the inflammasome, resulting in IL-1β production and impaired glucose tolerance and insulin sensitivity[70]. The inflammasome is composed of NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) and the adaptor protein ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain). Deletion of NLRP3 or ASC or pharmacological inhibition of caspase-1 (ref. 71) can protect against HFD-induced insulin resistance and glucose intolerance.

Abundance of IL-6 also positively correlates with obesity-induced insulin resistance[72], and many reports have suggested that IL-6 has proinflammatory effects[73,74]. However, there are also studies that have described anti-inflammatory actions of IL-6 (refs. 75–77). Whether IL-6 has positive or negative effects on metabolism is still controversial, and these discrepancies could be partly explained by tissue-specific effects of IL-6 on insulin action, such that its effects on insulin sensitivity would be detrimental in liver and adipose but beneficial in skeletal muscle[78]. Other proinflammatory cytokines such as IL-18, C-X-C motif chemokine-5 (CXCL5), angiopoietin-related protein 2 and lipocalin 2 may contribute to inflammation in the context of metabolic disease[46].

Proinflammatory cytokines also induce changes in gene expression that can affect metabolic regulation. For example, TNF-α treatment of adipocytes results in decreased expression of the insulin-responsive glucose transporter GLUT4 (ref. 79) and PPAR-γ[80]. As an additional mechanism, proinflammatory cytokines and saturated fatty acids can lead to upregulation of the genes involved in ceramide biosynthesis[81], consistent with earlier work that showed positive correlations between the amounts of cytokines and ceramide in plasma and insulin resistance[82]. Ceramide promotes dephosphorylation of Akt (PKB) by protein phosphatase 2A[83], resulting in impaired insulin signaling and insulin resistance. Holland *et al.*[81] showed that increased ceramide production was not required for Toll-like receptor 4 (TLR4)-dependent induction of inflammatory cytokines, but it was essential for TLR4-dependent insulin resistance, providing a key link between inflammatory pathway–induced lipid signaling and decreased insulin action. Many other genes are associated with insulin resistance, and whole-genome expression signatures have been defined that are enriched in inflammatory gene modules in insulin-resistant mice and humans[84,85].

Cytokines exert largely local paracrine effects, but if their levels in tissue are high enough, they can leak out into the systemic circulation. However, in inflammatory states, the tissue concentrations of cytokines are likely to be much higher than the circulating concentrations, and it remains to be shown whether the typical blood concentrations of circulating proinflammatory cytokines in obesity or type 2 diabetes are sufficient to exert endocrine effects on systemic insulin sensitivity.

Anti-inflammatory cytokines. In addition to the proinflammatory cytokines, anti-inflammatory cytokines are elevated in obesity, including IL-1Ra[86], secreted frizzled-related protein 5 (SFRP5)[87] and IL-10 (ref. 87). IL-1Ra can block IL-1β signaling, and SFRP5 inhibits the Wnt pathway by sequestering Wnt proteins and preventing them from binding their receptors. IL-10 can inhibit the deleterious effects of proinflammatory cytokines on insulin signaling[88]. Furthermore, *in vivo* administration of IL-10 prevents the development of IL-6– or lipid-induced insulin resistance[89], and muscle-specific transgenic overexpression of IL-10 increases whole-body insulin sensitivity[49,90].

In summary, high expression of proinflammatory cytokines is associated with insulin resistance, and the homeostatic balance between

Table 1 Genetic studies in mice showing the contribution of immune cell–mediated inflammation in obesity-induced insulin resistance

Type of genetic modification	Affected gene product	Phenotype of knockout mouse	Ref.
Myeloid-specific LysM-Cre	IKK-β	Protected from insulin resistance	57
	HIF-1α	Impaired macrophage migration	140
	PPAR-γ	Increased insulin resistance, glucose intolerance	60,61
	IR	Protected from inflammation and insulin resistance	58
	ABCA1 (ATP-binding cassette transporter)	Increased proinflammatory response of macrophages	158
	SOCS1 (suppressor of cytokine signaling 1)	Increased inflammation and hepatic insulin resistance	159
	PPAR-δ	Insulin resistant	91,160
Bone marrow transplantation	TLR4	Improved insulin sensitivity	161
	CAP (Cbl-associated protein, encoding gene: *Sorbs1*)	Protected against insulin resistance	162
	FABP4 and FABP5	Improved insulin sensitivity	59
	CXCR2 (also called KC receptor)	Reduced numbers of ATMs and improved insulin sensitivity	163
	JNK1	Protected against inflammation and insulin resistance	20
	PKC-ζ (Protein kinase C-ζ)	Inflammation and insulin resistance caused by PKC-ζ ablation in the nonhematopoietic compartment	164
	KLF4 (Kruppel-like factor 4)	Insulin resistant	165
	IL-10	Insulin resistance not affected	166
Whole body	α_4 integrin	Protected against insulin resistance	167
	CCR2	Decreased ATM content and improved insulin resistance	34
		No change in ATM content in obesity	35
	Cbl-b (Casitas B-lineage lymphoma b)	Increased numbers of ATMs and insulin resistance	168
	BLT1	Protected against insulin resistance	38
	TNF-α	Protected against insulin resistance	14
	IL-1R1	Protected against inflammation and insulin resistance	169
	GPR120	Loss of omega-3 mediated anti-inflammatory and insulin-sensitizing effects	55
	NLRP3	Protected against insulin resistance	70
	ASC	Protected against insulin resistance	70
Transgenic expression in macrophages	$CD11c^+$ macrophage ablation	Improved insulin sensitivity	53
Other immune cells	Eosinophil	Increased inflammation and insulin resistance	128
	T cells	Development of obesity and insulin resistance	120–122
	Mast cell	Attenuated inflammatory responses and improved glucose homeostasis	127
	B cell	Protected against insulin resistance	125

pro- and anti-inflammatory cytokines defines the profile and magnitude of inflammation and its effects on insulin sensitivity and glucose homeostasis.

Obesity leads to inflammation in other tissues

Development of hepatic insulin resistance. The liver is the major site of endogenous glucose production, and hepatic insulin resistance involves inadequate insulin-mediated suppression of hepatic glucose output, which has a pivotal role in the pathogenesis of type 2 diabetes. Notably, in obesity the liver manifests mixed insulin resistance, as the effects of insulin on suppressing glucose output are impaired but its lipogenic effects are accentuated. As in adipose tissue, in the liver obesity leads to an increase in proinflammatory gene expression[23]. Proinflammatory pathways in Kupffer cells, the resident hepatic macrophages, are activated in obesity, although the total number of Kupffer cells does not seem to be increased[23]. Kupffer cells can change their activation state from a classical proinflammatory state to an anti-inflammatory, alternatively activated, state. For example, in response to IL-4, PPAR-δ directs Kupffer cells to express an alternative macrophage phenotype, thereby ameliorating obesity-induced insulin resistance[91]. Recent studies have also described a macrophage population, distinct from Kupffer cells, that is recruited to the liver from circulating monocytes during the development of obesity in a manner similar to the recruitment observed in adipose tissue[92]. Like those secreted by adipose tissue, the inflammatory cytokines released by liver macrophages can activate proinflammatory pathways in hepatocytes, thereby causing hepatic insulin resistance. For example, activation of IKK-β in the hepatocyte leads to systemic insulin resistance[23], and hepatocyte-specific ablation of IKK-β protects mice from insulin resistance[57]. Depletion of Kupffer cells and recruited hepatic macrophages using gadolinium[93] or clodronate[94] shows that liver macrophages are a causal factor in obesity-induced hepatic insulin resistance. However, the distinct function of Kupffer cells versus that of recruited hepatic macrophages is not yet well understood.

Development of muscle insulin resistance. Skeletal muscle accounts for 70–80% of postprandial glucose uptake[95], and, therefore, muscle insulin resistance has a profound effect on glucose intolerance and hyperglycemia in obesity and type 2 diabetes. Intramuscular adipose tissue depots are present between muscle fibers, and macrophages are recruited to these adipose tissue depots[90]. Many cytokines, including TNF-α, IL-1β and IL-6 (ref. 96), can be produced in muscle tissue (either by myocytes or macrophages), and it is possible, although not yet proven, that these cytokines could contribute to local insulin resistance[97].

Inflammation and metabolism in non-classical insulin target tissues. Obesity-induced inflammatory changes have also been reported in the central nervous system (CNS), including in the hypothalamus[98]. The hypothalamus is the control center for regulating whole-body energy

homeostasis, and central insulin[98] and leptin[99] signaling are crucial to this process. Microglia are the resident macrophages in the CNS and share many functions with peripheral tissue macrophages, including their ability to carry out phagocytosis and release various cytokines, including TNF-α, IL-1β and IL-10 (refs. 100,101). Microglia can be activated by proinflammatory signals, resulting in the production of cytokines that act locally on other CNS cell types. It has been proposed that hypothalamic inflammation has a role in central leptin resistance through cytokine-mediated inhibition of signal transducer and activator of transcription-3 (STAT3), which is a key component of the leptin signaling pathway. Indeed, recent studies have demonstrated that activators of IKK-β and NF-κB in the hypothalamus can mediate leptin resistance[102]. Obesity is associated with leptin resistance, and studies have indicated that attenuation of the central effects of leptin can further promote obesity.

Increased numbers of macrophages have been observed in the pancreatic islets of HFD-fed rodents as well as in islets from individuals with type 2 diabetes[103]. Pancreatic islets secrete cytokines, notably IL-1β, the concentration of which is elevated in humans with type 2 diabetes[104] and can cause impaired insulin secretion and promote pancreatic β-cell apoptosis[105]. On the basis of these findings, it is possible that a heightened inflammatory response in islets has a role in the β cell dysfunction characteristic of type 2 diabetes, and a number of clinical studies have explored the effects of antagonizing IL-1β[106].

A large and important body of literature has recently emerged that describes the interconnections between diet, gut microflora and immune cell status and the spectrum of obesity, inflammation and insulin resistance. This subject has been extensively reviewed[107,108]. It is likely that the gut microbiome plays a part in the development of obesity as well as in the tissue inflammatory responses that contribute to insulin resistance and glucose intolerance. For example, in obesity, the epithelial layer of the gut becomes leaky, allowing microflora-derived products access to the systemic circulation, and high circulating levels of the potent TLR4 agonist lipopolysaccharide (LPS) in obese states have been well documented[109]. Furthermore, in obesity the bacterial composition of the gut also changes in a process called dysbiosis. In mice, the modulation of gut microbiota by antibiotic treatment is associated with a reduction in inflammatory marker expression by fat tissue and improvements in glucose tolerance[110,111].

The primacy of adipose tissue. Systemic insulin resistance in obesity can be initiated largely in adipose tissue, and macrophage-mediated tissue inflammation is a core mechanism of this aspect of adipose tissue dysfunction. Adipose tissue can communicate with the liver and muscle through the release of cytokines, adipokines and fatty acids and, possibly, through other signals that have yet to be identified, thus leading to effects on systemic inflammation and insulin sensitivity. Tissue-specific knockout mice have provided a powerful way to dissect the complex and interacting pathways involved in these processes and to distinguish direct from indirect effects. Genetic manipulations in adipocytes that improve adipocyte insulin sensitivity typically lead to systemic insulin sensitivity, with enhanced insulin actions in liver and muscle. For example, adipocyte-specific ablation of JNK1 (refs. 74,112) or overexpression of dominant-negative cAMP response element–binding protein (CREB)[113] or constitutively active PPAR-γ[114] result in improved insulin sensitivity in adipose tissue and have systemic effects that augment hepatic and skeletal muscle insulin sensitivity. Furthermore, adipose-specific deletion of GLUT4 (ref. 115) or overexpression of MCP-1 (ref. 116) results in systemic impairment of insulin sensitivity. Conversely, local changes in insulin sensitivity in liver[57,117] or muscle[118,119] often remain tissue autonomous and are not communicated to other insulin target tissues. Thus, adipose tissue is often referred to as the master regulator in the development of systemic insulin resistance.

The role of other immune cells in insulin resistance

Recent studies have revealed a growing list of immune cells other than macrophages that infiltrate adipose tissue and have potential roles in insulin resistance (**Fig. 2**). In the complex *in vivo* situation, it is likely that there is a great deal of regulatory intercommunication among these cell types in obesity and insulin-resistant states. Although more information is needed to determine the precise function of each immune cell type in insulin resistance, it seems likely that these cells exert their main effects by changing the recruitment, polarization or activation state of ATMs, such that the M1-like ATMs would be the ultimate effector cell of insulin resistance. There is considerable interest in which specific immune cell type in adipose tissue has the largest role in insulin resistance. As obesity develops, the enlarging adipocyte secretes chemokines to attract immune cells, and this is likely to be the initiating event. It is clear that macrophages arrive early, as their numbers increase after 1 week of exposure to a HFD[48], but the early sequence of events involving other immune cells remains to be carefully defined. In the context of obesity, various mechanisms stimulate the release of several factors from multiple cell types (adipocytes, lymphocytes, mast cells and eosinophils) that influence the overall recruitment, residence and accumulation of ATMs. It is important to remember that in the physiological setting for the development of obesity, these factors function mostly at the same time and in an integrated, concerted manner, rather than in an isolated, linear process.

Lymphocytes. T cells in adipose tissue are believed to play a part in obesity-induced inflammation by modifying ATM numbers and their activation state[120–122]. T helper (T_H) cells express the surface marker CD4 and can be divided into two distinct cell populations: T_H1 cells, which produce proinflammatory cytokines, and T_H2 cells, which produce anti-inflammatory cytokines[123]. Another $CD4^+$ population, regulatory T cells (T_{reg} cells), which also express forkhead–winged-helix transcription factor (Foxp3), can secrete anti-inflammatory signals, inhibit macrophage migration and induce M2-like macrophage differentiation. The number of adipose tissue T_{reg} cells decreases with obesity[120,122], and a boost in the number of these cells in obese mice can improve insulin sensitivity[120]. Winer *et al.*[122] suggested that lymphocytes may have a protective role against insulin resistance, as RAG-1–deficient mice, which lack T lymphocytes, developed a greater degree of insulin resistance relative to controls when fed a HFD. T cells that express the surface antigen CD8, referred to as effector, or cytotoxic, T cells, also secrete proinflammatory cytokines. Nishimura *et al.*[121] have shown that in obese adipose tissue, $CD8^+$ T cells are increased and promote the recruitment and activation of ATMs. The anti-inflammatory properties of T_{reg} cells and T_H2 $CD4^+$ cell populations and the proinflammatory nature of T_H1 and $CD8^+$ cells was confirmed by adoptive transfer experiments showing that $CD4^+$, but not $CD8^+$, T cells normalized glucose tolerance in RAG-1–deficient mice[122].

The temporal pattern of T cell and macrophage recruitment to adipose tissue during the development of obesity and insulin resistance is not yet fully understood. Nishimura *et al.*[121] proposed that adipose tissue T_H1 cells may initiate an inflammatory cascade before ATM infiltration. However, Strissel *et al.*[124] recently found that the number

of T_H1 cells did not increase until 20 weeks after introduction to HFD, several months after the increase in ATMs and insulin resistance. Whatever the time course of inflammatory cell recruitment, although T cells clearly have a role in the development of inflammation and insulin resistance *in vivo*, they are not absolutely essential to the process, as obese mice depleted of lymphocytes can still mount an ATM-mediated inflammatory response and develop decreased insulin sensitivity.

B cells can also accumulate in visceral adipose tissue in HFD-fed obese mice[125]. B cell recruitment can promote the activation of T cells that potentiate M1-like macrophage polarization and insulin resistance. Furthermore, B cells can cause systemic effects through the production of pathogenic IgG autoantibodies[125].

Mast cells. A role for mast cells in obesity was suggested in 1963 on the basis of the observation that there were increased numbers of mast cells in adipose tissue of obese hyperglycemic mice[126]. This finding was recently confirmed in obese mice and humans by Liu *et al.*[127]. These authors also showed that genetic depletion or pharmacological stabilization of mast cells in mice reduced body weight gain, attenuated inflammatory responses and improved glucose homeostasis[127].

Eosinophils. Adipose tissue eosinophils may have a role in sustaining the M2-like ATM polarization state, and, in obesity, the adipose tissue content of eosinophils is greatly decreased[128]. Eosinophils are the main cells expressing IL-4 and IL-13 in white adipose tissue, and, in their absence, the number of M2-like ATMs is greatly reduced. For example, mice that are genetically deficient for eosinophils show more inflammation and insulin resistance than wild-type mice on a HFD. Furthermore, helminth-induced elevations in eosinophil counts were associated with improved glucose tolerance in HFD-fed obese mice, suggesting that by promoting the M2-like ATM polarization state, eosinophils help to control adipose tissue inflammation and promote normal insulin sensitivity. In this way, decreased adipose tissue eosinophils in obesity could contribute to inflammation and insulin resistance.

Signals that stimulate or reduce inflammation

Chronic caloric excess leads to adipose tissue expansion, and enlarging adipocytes secrete chemokines that stimulate macrophage migration, initiating the tissue inflammatory response. The earliest signals that start this process are of great interest. Nutrient surplus can also trigger intracellular stress signals that potentiate proinflammatory signaling once it has been initiated, as summarized in **Figure 4**. For example, protein biosynthetic pathways are increased in obesity, overloading the protein-folding capacity of the endoplasmic reticulum (ER). The disruption in ER homeostasis is sensed by three different molecular components referred to collectively as the unfolded protein response (UPR). These three components are inositol-requiring protein-1 (IRE1), activating transcription factor-6 (ATF6) and double-stranded RNA–dependent protein kinase (PKR)-like ER kinase (PERK). Together, they regulate the expression of numerous genes in an attempt to alleviate ER stress[129]. The UPR can also stimulate proinflammatory pathways. For example, IRE1, which activates chaperone genes in response to ER stress, also stimulates JNK[130], resulting in increased serine phosphorylation of IRS-1 and impaired insulin action. In related studies, an alternate pathway to JNK activation in obesity involves PKR, a close homolog of PERK. PKR can stimulate JNK activation in response to nutrient signals as well as to ER stress, leading to decreased insulin signaling[131]. Compounds that enhance

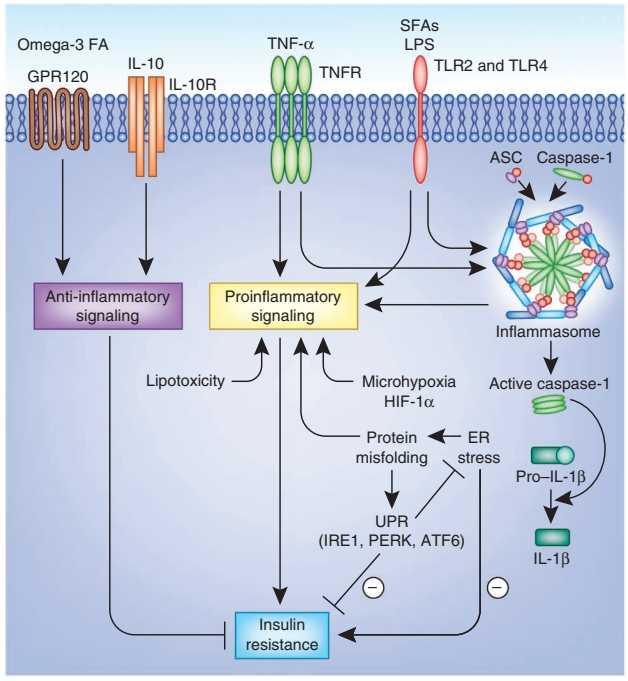

Figure 4 Signaling pathways that potentiate or reduce inflammatory signaling. Saturated fatty acids and cytokines (TNF-α) stimulate proinflammatory signaling. Hypoxia and ER stress further stimulate proinflammatory pathways leading to insulin resistance. Protein misfolding is sensed by three different molecular components (IRE1, PERK and ATF6) that are collectively referred to as the UPR. Anti-inflammatory signaling is mediated by IL-10 and omega-3 FAs at GPR120 to attenuate inflammation. The NLRP3 and ASC proteins form part of the inflammasome, which mediates catalytic activation of caspase-1, followed by cleavage of pro–IL-1β to IL-1β.

protein folding and stabilize protein conformation have been identified, and treatment of obese and diabetic mice with these 'chaperone mimics' leads to improved insulin sensitivity[132]. Further evidence that ER stress is linked to insulin resistance has been provided by genetic studies in mice. For example, deletion of X-box binding protein 1 (XBP1), a transcription factor that promotes the UPR, results in the development of insulin resistance[133].

ER stress can trigger autophagy, an essential homeostatic process whereby the cell breaks down its own components to help maintain a balance between the synthesis, degradation and subsequent recycling of cellular products. Recent reports have shown that the failure of autophagy-dependent control of immune-cell homeostasis can contribute to inflammation and insulin resistance[134,135].

It is well established that obesity leads to increased adipocyte size and that some of these enlarged adipocytes undergo necrotic cell death and become surrounded by macrophages in crown-like structures. Although it is tempting to infer that adipocyte necrosis triggers an inflammatory response, the concomitant presence of these enlarged necrotic adipocytes and ATMs is at present simply an association. Whether necrosis triggers inflammation or inflammation causes necrosis remains to be addressed. Indeed, Feng *et al.*[136] have recently demonstrated that HFD-induced adipocyte cell death is an intrinsic cellular process and is not triggered by macrophage infiltration or activation. More importantly, they showed that when adipocyte necrosis is blocked by deletion of cyclophilin D, obesity-mediated ATM accumulation and inflammation still occur. Additionally, Li *et al.*[54] showed that ATM accumulation preceded detectable adipocyte

necrosis in the early phase of a HFD. Therefore, both of these studies argue that adipocyte necrosis is uncoupled from inflammation.

During the development of obesity, the supply of oxygen to the expanding adipose tissue mass becomes inadequate, resulting in areas of microhypoxia. This phenomenon of poorly oxygenated adipose tissue, first observed in mice, is also present in obese humans[137]. Hypoxia activates the transcription factor hypoxia-inducible factor-1α (HIF-1α), which induces expression of proinflammatory cytokines[138]. Macrophage HIF-1α activation is also necessary for the energy generation needed for macrophage migration, and deletion of HIF-1α from adipocytes partially protects mice from HFD-induced obesity and insulin resistance[139]. Macrophage-specific deletion of HIF-1α impairs macrophage migration *in vivo* in a model of chronic cutaneous inflammation, but further studies are necessary to determine the role of macrophage HIF-1α in inflammation-induced insulin resistance[140].

Exogenous signals can also modify inflammatory responses. Systemic levels of saturated fatty acids (SFAs) are increased in obesity, and through TLR4-dependent effects SFAs can induce inflammatory cascades in macrophages, adipocytes, muscle and liver[109]. In obesity, LPS derived from the gut microflora can leak into the circulation, resulting in higher serum LPS concentrations[141], and LPS signals through TLR4 to stimulate secretion of proinflammatory cytokines[142]. Conversely, omega-3 fatty acids exert strong anti-inflammatory effects by signaling through G protein–coupled receptor-120 (GPR120), resulting in improved insulin sensitivity in obese mice[55].

Clinical anti-inflammatory strategies

The clearest proof of concept that an anti-inflammatory strategy may prove successful in the treatment of insulin resistance has come from studies using salicylates. High-dose salicylates administered to obese mice inhibit NF-κB activity, leading to improved insulin sensitivity and glucose metabolism[16]. In humans, salicylate treatment enhanced insulin sensitivity in a small group of subjects with diabetes[143], and this prompted a larger clinical trial in which salsalate treatment resulted in lowered glycated hemoglobin levels and improved glycemic control[144]. Larger, extended trials are now ongoing to determine the full therapeutic potential of salicylate therapy in type 2 diabetes.

Another more widespread therapeutic approach to modulating the immune system involves TZDs. TZDs are PPAR-γ ligands with well-known insulin-sensitizing effects in the clinical setting. These compounds also have potent anti-inflammatory actions that contribute to the overall improvement in insulin resistance with type 2 diabetes treatment[145,146]. However, TZDs are also associated with several adverse effects, including weight gain, edema-increased risk of bone fracture and, in some cases, an increased incidence of heart disease[147].

Other anti-inflammatory strategies are still without definitive proof of concept. For example, many reports have described the role of TNF-α in insulin resistance[12,14]. Blocking this cytokine improved insulin resistance in rodents[13], but neutralizing antibodies to TNF-α had only marginal effects on fasting glucose levels in obese patients[148]. The lack of efficacy of TNF-α–targeting treatments in humans is now being studied and might be a consequence of insufficient concentrations of neutralizing antibody reaching the interstitial adipose tissue space, where TNF-α levels are particularly high. However, a recent study found that patients receiving TNF-α inhibitors for systemic inflammatory conditions, including rheumatoid arthritis and psoriasis, had a significantly decreased risk of developing type 2 diabetes compared with patients taking other antirheumatic drugs, suggesting that anti–TNF-α strategies might be effective in disease prevention[149].

Several clinical studies have been conducted using different strategies to inhibit IL-1 signaling. Studies in rodents[150,151] and humans[152] have shown that blockade of IL-1 action results in a modest improvement in glycemic control attributable to enhanced B cell function, but insulin sensitivity was not increased[153]. Additional clinical trials based on IL-1 receptor blockade or IL-1β–specific antibodies are ongoing and have been recently reviewed[106]. Promising preliminary results have been reported in a phase 2 clinical trial treating patients with type 2 diabetes with an oral CCR2 antagonist (CCX140-B, ChemoCentryx). These studies showed that, over 4 weeks of treatment, administration of the CCR2 antagonist led to a significant decrease in fasting glucose levels and glycated hemoglobin (HbA1c)[154]. It is somewhat surprising that, despite the pressing need for increased antidiabetic therapeutics and substantial interest in pursuing such therapies from pharmaceutical companies, there are relatively few anti-inflammatory strategies for the treatment of metabolic disease with published clinical trial data.

Unanswered questions, future directions and concluding remarks

The realization that inflammatory signaling and metabolic signaling are closely linked has given rise to the concept of immunometabolism. In this emerging field there are many exciting ideas and unanswered questions to be addressed with further research.

Inflammation-induced insulin resistance can be viewed as a two-hit process. First, activated immune cells accumulate in tissues and release proinflammatory cytokines. These cytokines then act on neighboring insulin target cells (the second hit), causing decreased insulin sensitivity. Signaling through Toll-like receptors, the TNF-α receptor or any signal-dependent proinflammatory stimulation typically activates a broad range of intracellular cascades that includes stimulation of IKK-β, NF-κB, JNK1 and AP1. Thus, signal-dependent mechanisms can commonly activate a number of interconnected, often overlapping, intracellular proinflammatory pathways. Consequently, therapeutic interventions designed to inhibit a particular component in one of these pathways may not yield robust effects on a complex process such as insulin resistance, owing to the redundancy of these signaling networks. Therefore, the most effective strategies will probably be targeted at proximal and common steps in these pathways or be directed at pathophysiologic mechanisms that are of core importance to the etiology of inflammation-induced insulin resistance.

Thus far, therapeutic strategies that rely on targeting single cytokines or receptors (for example, TNF-α and IL-1) have had limited success in humans, suggesting that targeting upstream components rather than single cytokines could provide a more effective therapeutic approach. For example, inhibition of IKK-β, JNK or—perhaps even better—some more proximal element in the proinflammatory pathway could be a useful strategy. However, a general concern with broad anti-inflammatory therapies is whether they could adversely compromise immune system responses. A more specific approach that selectively targets the proinflammatory M1-like, and not the M2-like, macrophages could provide therapeutic benefits without inhibiting other innate immune functions. For example, a treatment based on a proinflammatory protein target expressed primarily in M1 macrophages (for example, GPR120), could provide improved specificity. Alternatively, selectivity could be achieved by inhibiting macrophage chemotaxis, as >90% of monocytes that migrate into obese adipose tissue become M1-like ATMs, whereas M2-like ATMs may be derived from the proliferation of resident cells. Finally, a treatment that boosts the number of resident M2-like macrophages

could also redirect the ATM balance to a less proinflammatory state and improve inflammation-induced insulin resistance.

It is evident that an appropriate anti-inflammatory therapeutic approach could be an effective treatment for type 2 diabetes. However, because obesity-associated inflammation and insulin resistance represent early abnormalities in the progression toward diabetes, inhibiting inflammatory responses might be particularly important for diabetes prevention[155]. Any successful preventative treatment must include clearly defined and robust selection criteria to predict those individuals who are at greatest risk of developing type 2 diabetes. Such a treatment should be effective at preventing insulin resistance but must also be particularly safe with minimal side effects, as some fraction of the 'at-risk' prediabetic population will not actually progress to diabetes, even in the absence of treatment.

Within the general field of immunometabolism, a number of rapidly evolving areas present exciting opportunities for the future. For example, gastric-bypass surgery is well known to cause rapid improvement in insulin sensitivity and glucose tolerance, and recent studies have shown that bariatric surgery results in a marked reduction of proinflammatory markers independent of body weight loss[156]. This suggests interconnections between these surgical methods and the immune system that are not understood; more knowledge in this area could lead to new insights with therapeutic potential. Certainly, these observations could relate to the gut microflora. The interface between the enormous, complex and diverse intestinal microbial community and obesity, insulin resistance and glucose tolerance is an exciting research frontier. The gut microbiome changes with obesity, leading to more efficient use of calories and nutrients, and many studies have indicated that the gut microflora could be a new target for therapeutic intervention[107,157]. A key aspect of research in this area will be to gain a better understanding of how changes in the microbiota affect the development of inflammation and how environmental influences affect the microbiota.

More knowledge is needed about the factors that direct the polarization state of macrophages toward either the pro- or anti-inflammatory state, as this could also be a key nexus for therapeutic intervention. The story of adipose tissue inflammation clearly goes beyond macrophages, and there are likely to be many more unexpected findings as the field learns about the complex interactions between the various immune cell types that populate adipose tissue.

The liver is the main site of endogenous glucose production, and skeletal muscle is the main organ of insulin-mediated glucose disposal. How these tissues fit into the picture of immunometabolism needs much further study, as these organ systems are largely responsible for overall glucose homeostasis. The liver is heavily populated with immune cells, including Kupffer cells, recruited macrophages, lymphocytes and neutrophils. Are these cell types the primary contributors to hepatic insulin resistance, or are they secondary recipients of inflammatory signals arising outside the liver? Inflammatory programs can be activated within skeletal muscle cells in obesity, but how does this occur? In obesity, intermuscular adipose tissue depots form that contain macrophages and other immune cell types. Do the cytokines secreted from these depots directly affect muscle metabolism, or do the proinflammatory signals come from more distal sites or involve processes unrelated to inflammatory pathways?

Finally, despite enormous efforts, researchers still have a very poor understanding of how genetic determinants interact with the environment and lead to the development of metabolic diseases. Large genetic studies that include more sophisticated phenotypic analyses are needed so that the manner in which genetic susceptibilities allow nutrition and other environmental factors to cause insulin resistance and diabetes can be better understood. In addition to identification of susceptibility genes, these studies should also focus more intently on identifying protective alleles, which could help to explain why not all people with obesity are resistant to insulin and why many insulin-resistant subjects do not develop diabetes. Environmental factors can influence gene expression through epigenetic changes, and it is likely that comprehensive studies of the epigenome will be required to fully understand gene-environment interactions in obesity and type 2 diabetes. As in most fields of science, it is likely that many facets of the next round of breakthroughs will bring some welcome surprises.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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