Macrophages are key innate immune effector cells best known for their role as professional phagocytes, which also include neutrophils and dendritic cells. Recent evidence indicates that macrophages are also key players in metabolic homeostasis. Macrophages can be found in many tissues, where they respond to metabolic cues and produce pro- and/or anti-inflammatory mediators to modulate metabolite programmes. Certain metabolites, such as fatty acids, ceramides and cholesterol crystals, elicit inflammatory responses through pathogen-sensing signalling pathways, implicating a maladaptation of macrophages and the innate immune system to elevated metabolic stress associated with overnutrition in modern societies. The outcome of this maladaptation is a feedforward inflammatory response leading to a state of unresolved inflammation and a collection of metabolic pathologies, including insulin resistance, fatty liver, atherosclerosis and dyslipidaemia. The present review summarizes what is known about the contributions of macrophages to metabolic diseases and the signalling pathways that are involved in metabolic stress-induced macrophage activation. Understanding the role of macrophages in these processes will help us to develop therapies against detrimental effects of the metabolic syndrome.

Key words: inflammatory signalling, insulin resistance, macrophage activation, metabolic disease, metabolic syndrome, white adipose tissue inflammation.

INTRODUCTION

The innate immune system, which consists of macrophages, dendritic cells and a variety of other effector cells, has evolved as a formidable defence against external threats to the human host. When first described by Elie Metchnikoff in the late 1800s, macrophages were thought to primarily function as phagocytes. In the next several decades, intense effort went into understanding the mechanisms that led to macrophage activation. It was not until about 100 years later that researchers first started to document the innumerable roles that macrophages play [1]. We now know that macrophages are found throughout the body and are involved in tissue homeostasis, wound healing, general surveillance of host threats and, as was first observed, killing of foreign pathogens.

Abundant sources of food that have high energy content and are enriched in saturated fats, coupled with a lack of physical activity, are responsible for the sharp increase in a collection of pathologies, such as obesity, hepatosteatosis, insulin resistance and atherosclerosis, known as the metabolic syndrome. All of these pathologies increase the chance of developing cardiovascular disease, diabetes mellitus and premature death [2]. The observation that anti-inflammatory salicylates could improve insulin sensitivity and glucose responsiveness gave the first indication that metabolic syndrome is associated with low-grade chronic inflammation [3]. This was followed by reports that inflammatory cytokines, such as TNFα (tumour necrosis factor α), inhibit insulin responsiveness in adipocytes, providing a link between inflammation and metabolic pathways [4–6]. Subsequent studies have suggested that lipid overload triggers the immune system, especially macrophages, to respond in a deleterious manner, in which a resolution state could not be achieved [7,8]. At around the same time as these studies were occurring, researchers observed that insulin resistance and hyperglycaemia led to dysregulated immune responses and increased incidences of infection in patients with the metabolic syndrome [9–16]. Together, it has become evident that metabolic pathways are tightly intertwined with inflammatory signalling and immune responses.

As environmental sentries, it is not surprising that macrophages sense and regulate metabolism. This link between macrophages and metabolic regulation was strengthened further with the discovery of resident macrophage populations in metabolically active tissues, such as WAT (white adipose tissue) and liver [17,18]. The interplay between resident macrophages and pathologies associated with the metabolic syndrome has been studied extensively since. In the present review, we highlight major contributions of macrophages to the metabolic milieu and describe how the functions of macrophages are altered during states of metabolic dysfunction. We begin with a brief overview of the recruitment of macrophages in various metabolic tissues and the diseases associated with their activation. We then discuss some proposed mechanisms for the inflammatory pathways that lead to pathologies, with an emphasis on insulin resistance/Type 2 diabetes.

AN ESSENTIAL ROLE FOR MACROPHAGES IN METABOLIC PATHOLOGIES

Resident macrophages in different tissues adapt to their local microenvironment and exhibit diverse functional and...
The production of chemokines, the factors that recruit immune cells to sites of trouble, is increased in states of metabolic dysfunction. MCP-1 (monocyte chemoattractant protein 1) [also known as CCL2 (CC chemokine ligand 2)] and its receptor CCR2 (CC chemokine receptor 2) are the most studied chemokine signalling molecules in metabolic diseases. Earlier studies have demonstrated that MCP-1- and CCR2-knockout mice are protected from atherosclerosis [19–21]. CCR2-knockout mice also display attenuated macrophage accumulation and chronic inflammation in adipose tissue [22]. In addition, mice lacking MCP-1 or expressing a dominant-negative form of MCP-1 show improved insulin sensitivity [23], whereas transgenic MCP-1 overexpression in adipose tissue causes insulin resistance and hepatic steatosis [23,24]. Other chemokines, such as osteopontin, angiopoietin-like protein 2 and CXCL14 (CXC chemokine ligand 14) have also been shown to play a role in obesity-induced macrophage recruitment [25–28]. These studies demonstrate that macrophage infiltration is an essential step for metabolic disease pathogenesis.

**Activation**

Macrophages respond to many different types of foreign and host-derived stimuli and exhibit very precise and co-ordinated activation states according to the signals they receive. These states lie on a spectrum ranging from the pro-inflammatory state to the anti-inflammatory state [29] (Figure 2). Foreign pathogens or Th1 cytokines [e.g. TNFα, IL (interleukin)-1β and IFNγ (interferon γ)] transduce signals that activate macrophages to a pro-inflammatory phenotype, typically referred to as an M1 response, characterized by the expression of inflammatory markers, such as TNFα, IFNγ and iNOS (inducible nitric oxide synthase) [29]. In contrast, M2 macrophages, induced by Th2 cytokines IL-4 and IL-13, produce anti-inflammatory mediators, notably IL-10 [29]. As discussed below, the M1/M2 paradigm also applies to metabolic regulation, with M1 inducing and M2 preventing metabolic diseases respectively (Figure 3). Interestingly, dietary fatty acids are able to polarize macrophages towards M1 or M2 activation states, depending on the signalling molecules with which they interact (Figure 2), thus providing a molecular basis for the cross-talk between metabolic and inflammatory pathways.

**Resolution/deactivation**

The initial pro-inflammatory response is terminated by anti-inflammatory cytokines, such as IL-10, which is induced by both M1 and M2 cytokines to deactivate macrophages and promote resolution [30–33]. Lack of this termination signal leads to persistent establishment of the inflammatory response [34–36]. Epidemiological studies have shown that polymorphisms in the IL10 gene are associated with obesity and metabolic diseases [37–39]. Furthermore, in patients with Type 2 diabetes, circulating monocytes express decreased levels of IL-10 [40]. IL-10 and other deactivating signalling molecules are also induced during effectorcytosis, a process by which macrophages engulf and clear apoptotic cells in an effort to prevent necrosis and suppress inflammation [41]. This process is thought to help remove oxidized lipids and cholesterol and to activate Akt and NF-κB (nuclear factor κ B) survival pathways [42]. Several studies have shown that efficient effectorcytosis is necessary to inhibit necrotic plaque formation and defects in effectorcytosis lead to the formation of unstable lesions and an increase in systemic inflammation [43–46]. Faulty effectorcytosis has also been observed in diabetic mouse models and is thought to promote inflammatory signalling [47]. Oxidative stress and macrophage insulin resistance are two of the potential mechanisms that cause defective effectorcytosis [41,48]. Therefore the combined effects of persistent pro-inflammatory stimulation from increased lipid influx, decreased deactivating signals and compromised effectorcytosis lead to the unresolved inflammation in metabolic dysregulation.
Role and function of macrophages in the metabolic syndrome

Figure 2  Dietary lipids and inflammatory mediators share common signalling pathways in the control of macrophage activation

The Th2 (M2) type response, elicited by Th2 cytokines, notably IL-4 and IL-13, and parasitic worm infection, induces an anti-inflammatory phenotype in the macrophage and promotes metabolic homoeostasis, tissue repair, wound healing and angiogenesis. STAT6 is activated by Th2 cytokines to control the expression of PPARδ and PPARγ. Together, they regulate mitochondrial oxidative metabolism and macrophage alternative activation. The ω−3 fatty acids DHA and EPA are known to ligate the GPCR GPR120 to promote anti-inflammatory response. These fatty acids can also mediate PPAR activation. In contrast, saturated fatty acids (FAs), ceramides (metabolites of fatty acids) and cholesterol crystal can induce pro-inflammatory activation of the macrophage through pathogen-sensing proteins TLR2/TLR4, which activate the JNK cascade, leading to NF-κB relocation to the nucleus and induction of inflammatory cytokines and glycolytic pathways. Excess lipids have also been shown to induce ER stress and inflammasome activation. Pro-inflammatory cytokines produced by these macrophages, including TNFα and IL-1β, cause tissue damage and inhibit insulin signalling, which contribute to the pathogenesis of metabolic diseases. IκB, inhibitor of NF-κB; iNOS, inducible nitric oxide synthase.

Figure 3  Cross-talk between macrophages and adipocytes plays an important role in adipose tissue homoeostasis

In the physiological state, ATMs exhibit an M2 phenotype, mediated by the Th2 cytokines IL-4 and IL-13, and downstream transcription factors STAT6 and PPARδ/PPARγ. Several cell types within WAT have been reported to be the sources of Th2 cytokines, including T-lymphocytes, eosinophils and adipocytes. ω−3 fatty acids (FAs) are also able to induce an anti-inflammatory response through GPR120 and possibly PPARs. IL-10 is one of the well-characterized anti-inflammatory cytokines produced by these macrophages. In obesity, stressed adipocytes produce inflammatory mediators (e.g. MCP-1, TNFα and saturated fatty acids) to induce M1 activation through inflammatory transcription factors, such as NF-κB. Macrophages respond by up-regulating inflammatory cytokines, which activate JNK and inhibit insulin signalling pathways in the adipocyte.

Macrophages and metabolic pathologies

Macrophage infiltration and adipose tissue insulin resistance

The SVF (stromal vascular fraction) of WAT has been studied extensively in the progression of obesity-induced insulin resistance. Adipose tissues from lean animals and humans contain a resident macrophage population exhibiting the M2 phenotype [49] (Figure 3). In contrast, the obese state is characterized by infiltration of M1 macrophages that accumulate around apoptotic fat cells (referred to as crown-like structures) and express the CD11c marker [49]. It has been suggested that macrophages are recruited in response to adipocyte hypertrophy or to signals from dying adipocytes in an attempt to restore homoeostasis [50–52]. There they can be activated further by non-esterified...
fatty acids released by dysfunctional fat cells (discussed below), thus amplifying the inflammatory response. These macrophages contain lipid droplets derived from direct lipid intake or ingestion of dead fat cells and account for up to 40% of the SVF in severe cases of obesity [22]. They secrete pro-inflammatory factors, such as MCP-1, TNFα and IL-6, which both amplify inflammatory responses and inhibit adipocyte insulin signalling [17,18]. Similarly, monocytes from Type 2 diabetic patients or obese individuals express more M1 markers [40]. Conditional depletion of CD11c-expressing macrophages or inhibition of macrophage recruitment (e.g. MCP-1 knockout) in obese mice resulted in a significant reduction in systemic inflammation and an improvement in insulin sensitivity [23,24,53]. It should also be noted that adipocytes also produce inflammatory mediators. Because of similarities between adipocytes and macrophages, the source of the pro-inflammatory cytokines/chemokines within WAT is obscured. In contrast with WAT, macrophage infiltration into BAT (brown adipose tissue) seems to be limited and, as such, the role of macrophages in BAT is unclear [54,55].

Vascular inflammation and atherosclerosis

The most well-characterized macrophage population in the metabolic syndrome is that of macrophages recruited to sites of endothelial dysfunction in atherosclerosis [56,57]. Elevated LDL (low-density lipoprotein)/cholesterol levels result in accumulation of LDL particles in the subendothelial matrix. Careful analyses of temporal changes leading to lesion formation revealed that this lipid deposition is the crucial initiating event in macrophage recruitment [57]; the accumulated LDL becomes oxidized (oxLDL) and locally produced cytokines and chemokines, in response to oxLDL, recruit monocytes/macrophages into the subendothelial space. Lipid particles are taken up by macrophages through specialized receptors SR-A (scavenger receptor A) and CD36, among other mechanisms [58]. These processes evoke a characteristic inflammatory response by releasing inflammatory molecules, such as MCP-1, to the ECM (extracellular matrix), which recruit more macrophages. The lipid-laden macrophages become foam cells and undergo necrotic cell death releasing intracellular components leading to a vicious cycle of chronic inflammation [36]. Subsequently, smooth muscle cells migrate to the lesion in response to inflammatory mediators and contribute to fibrotic plaque formation and rupture [57].

Hepatosteatosis

Liver insulin resistance and hepatic steatosis, referred to as NAFLDs (non-alcoholic fatty liver diseases), are major components of the metabolic syndrome. Lipidomic analyses of liver tissue during various stages of NAFLD show a strong correlation between abnormal fat composition and disease pathogenesis [59], with excess fat accumulation leading to the recruitment of inflammatory cells [60]. Together with Kupffer cells, these immune cells are responsible for the development of hepatic inflammation in both humans and various animal models. Studies have shown that depletion of Kupffer cells or inhibition of pro-inflammatory mediators protect against the development of NAFLD [61–63]. During high-fat-diet treatment, depletion of Kupffer cells by GdCl3, or clodronate-encapsulated liposomes has been shown to improve insulin sensitivity and glucose tolerance [64–66]. A single dose of GdCl3 in mice on normal chow enhances insulin signalling and reduces glucose production in the liver [65]. In contrast, macrophage-specific Ppard−/− (peroxisome-proliferator-activated receptor δ) mice, whose macrophages/Kupffer cells exhibit a predominantly M1 phenotype, develop insulin resistance and hepatic steatosis [67].

Muscle dysfunction

The resident macrophage population in muscle has not been characterized. Macrophages do, however, play a significant role in muscle repair during exercise and tissue damage [68]. Studies have shown that macrophages infiltrate fat depots formed around the muscle in obesity [17]. Additionally, muscle can be affected by inflammatory cytokines from other tissues, such as liver and adipose tissue, even though it may not be a site of significant production of inflammatory mediators [69].

INFLAMMATORY SIGNALLING AND METABOLIC DISEASES

Although the role of inflammation in atherogenesis is well documented [36,56,57], the underlying mechanisms through which pro-inflammatory signalling pathways cause insulin resistance are still under investigation. One of the better-defined mechanisms is through JNK (c-Jun N-terminal kinase) activation, which phosphorylates IRS-1 (insulin receptor substrate-1) to block insulin signal transduction [7,70]. Similarly, our knowledge regarding how anti-inflammatory pathways improve metabolic homeostasis is limited, apart from their ability to antagonize M1 activation [71]. In this section, we summarize various signalling pathways mediating macrophage activation during the pathogenesis of the metabolic syndrome.

Pro-inflammatory signalling

JNK and pro-inflammatory cytokines

JNK is an important regulatory node for inflammatory mediators, including pro-inflammatory cytokines, TLRs (Toll-like receptors) and ER (endoplasmic reticulum) stress (Figure 2). In obesity-induced insulin resistance and hepatic steatosis, deletion of JNK1 in the haemopoietic compartment by bone marrow transplantation is beneﬁcial [72]. TNFα was one of the first pro-inflammatory cytokines to be linked to JNK activation [4,70]. TNFα-receptor-knockout mice show improved metabolic homeostasis and insulin sensitivity fed on both normal chow and a high-fat diet [73]. Additionally, Tnf−/− bone marrow donated to a Tnf−/− mouse induces insulin resistance in an otherwise insulin-sensitive mouse [74]. Recently, PKR (double-stranded RNA-dependent protein kinase), which senses viral infection, was shown to interact with JNK and IRS-1 [75]. Interestingly, PKR is able to phosphorylate IRS-1 directly, suggesting that JNK integrates different inflammatory signals through a multicomponent inflammatory complex.

TLRs and NF-κB

TLRs are pattern-recognition receptors that respond to pathogenic antigens and propagate inflammatory signalling [76]. In vitro, non-esterified fatty acids (saturated fatty acids, e.g. palmitic acid) or ceramides can signal through TLR2 and TLR4 on macrophages and induce pro-inflammatory gene expression [77–79]. In vivo, whole-body TLR4 deletion improves insulin sensitivity in a lipid-infusion model of transient insulin resistance. Similarly, TLR4 loss-of-function mutation or TLR2 deficiency protects against diet-induced obesity and insulin resistance [80–82]. However, TLR2 and TLR4 are expressed on most tissue types including adipocytes and hepatocytes, in addition to immune cells. The contribution of macrophage TLR4 was examined through haemopoietic cell-specific TLR4 deletion, which ameliorates high-fat diet-induced hepatic and adipose tissue insulin resistance [83].
TLR4 ligation promotes IKK (inhibitor of NF-κB kinase) activation, followed by phosphorylation and nuclear translocation of NF-κB to activate inflammatory gene transcription. Systemic deletions of NF-κB or various IKK isofoms (e.g. IKKβ and IKKα) prevent obesity-induced insulin resistance [36,84,85]. Myeloid-specific IKKβ deletion also leads to improved systemic insulin sensitivity, increased glucose disposal and suppressed hepatic glucose production [84]. In line with these observations, salicylate treatment, known to attenuate NF-κB activation, increases insulin sensitivity in humans [86–88].

In the setting of atherosclerosis, many studies have demonstrated that a complete deletion of various TLR family members reduces the lesion size in Ldlr−/− (low-density-lipoprotein receptor) or Apoe−/− (apolipoprotein E) mice [89,90]. Ldlr−/− mice transplanted with Tlr2−/− bone marrow are protected from atherosclerosis [89]. Similarly, Ldlr−/− mice deficient in myeloid-specific NF-κB subunit p50 have decreased atherosclerotic lesions [91]. Lesions in these animals exhibit near complete loss of foam cells, supporting previous findings that NF-κB regulates genes involved in lipid uptake and foam cell formation [92].

Inflammasome

The NLRP3 [NLR (nucleotide-binding-domain- and leucine-rich-repeat-containing) family, pyrin-domain-containing 3] inflammasome senses endogenous danger signals and generates the mature secreted forms of IL-1β and IL-18 through caspase 1 activation [93–96]. In vitro, palmitic acid and ceramide are able to induce IL-1β and caspase 1 processing in the macrophage [97]. Mice deficient in NLRP3 or ASC (apoptosis-associated speck-like protein containing a caspase-recruitment domain, an adaptor protein of the NLRP3 inflammasome) exhibit increased insulin sensitivity in liver, WAT and muscle [97–99]. In addition, caspase 1 and IL-1β have been shown to mediate inflammasome-induced insulin resistance [98]. Along these lines, lack of IL-1R, the receptor for IL-1β, confers protection against insulin resistance induced by a high-fat diet [100]. Inflammasome activation can also be detected in atherosclerotic lesions [101,102]. Cultured macrophages exposed to crystalline cholesterol secrete IL-1β and IL-18 [101,102]. In concert, Ldlr−/− mice transplanted with bone marrow from mice lacking NLRP3 or ASC show a reduction in the lesion area and IL-18 levels [101].

ER stress

The ER is the site of protein folding, vesicle transport and lipid synthesis. When the capacity of ER is overburdened, the UPR (unfolded protein response) is activated characterized by increased activities of PERK (PKR-like ER kinase), Ire1 (inositol-requiring enzyme 1) and ATF6 (activating transcription factor 6) [103]. Activation of the UPR through these signalling molecules leads to downstream CHOP (C/EBP CC/AAAT/enhancer-binding protein)-homologous protein) activation and subsequent induction of apoptosis. The initiation and propagation of the UPR and ER stress by obesity and metabolic stress have been reviewed in detail [103]. ER stress in adipose tissue or liver leads to insulin resistance, which is associated with activation of JNK and IKK, suggesting that ER stress is linked to inflammatory pathways [103–105]. In atherosclerosis, chronic activation of the ER stress pathway contributes to macrophage death and subsequent plaque necrosis [42]. CHOP expression and macrophage apoptosis have been correlated with advanced lesions [106,107], and deletion of CHOP suppresses lesional macrophage death/necrosis [108]. Lastly, it has been shown that the ER stress in the macrophage is caused by increased aP2 (adipocyte protein 2) lipid chaperone activity, which promotes atherogenesis [109].

Hypoxia

Activation of macrophages to a pro-inflammatory state increases glucose influx for glycolysis, which is controlled by HIF (hypoxia-inducible factor)-1α [110–113]. Loss of HIF-1α in the macrophage leads to decreased pro-inflammatory cytokine production, whereas deletion of VHL (von Hippel–Lindau tumour-suppressor protein), a repressor of HIF-1α, results in chronic activation of HIF-1α and uncontrolled inflammation [112,114]. In the context of metabolic dysregulation, adipose tissues in obese mice are hypoxic, which may cause macrophage HIF-1α activation [51,52,115,116]. Systemic hypoxia has been shown to induce insulin resistance and NAFLD [51,117,118]. Furthermore, high levels of hypoxia during adipose expansion may lead to necrotic death of both adipocytes and macrophages, since HIF-1α activation blocks physiological apoptotic cell death [52,116,119]. Similarly, hypoxia promotes macrophage necrosis in mouse models of atherosclerosis [119–121].

Anti-inflammatory signalling

Th2 cytokines

The other end of the macrophage activity spectrum is Th2 cytokine-induced alternative activation, characterized by the expression of M2 markers, such as Arg1, Mgl1 and Ym1 [29,71]. These macrophages function to repair damage elicited by pro-inflammatory M1 macrophages. As discussed above, in the lean state, ATMs display an M2 phenotype, suggesting that, at the physiological level, M2 macrophages may play an important role in metabolic homeostasis [49]. In line with this notion, Th2 cytokines, notably IL-13, have been detected in WAT and liver [122]. Treatment of diet-induced obese mice with IL-4 significantly improves glucose homeostasis and insulin sensitivity, whereas deletion of STAT6 (signal transducer and activator of transcription 6), a Th2 effector, worsens insulin resistance [123]. In addition, mice infected with helminth worms, which induce an M2 response, exhibit improved insulin sensitivity [124].

Nuclear receptors

Nuclear receptors are ligand-activated transcription factors that control important biological processes [125]. Several lipid-sensing nuclear receptors, such as the PPARs (PPARα, PPARδ and PPARγ, activated by dietary fatty acids) [126,127] and the LXR (liver X receptors) receptors (LXRA and LXRB, activated by cholesterol metabolites) are drug targets to treat metabolic diseases [128,129]. In the macrophage, IL-4/IL-13-induced alternative macrophage activation is associated with increased fatty acid β-oxidation and oxidative metabolism [122,130], pathways regulated by PPARs [131]. Accordingly, PPARδ and PPARγ have been shown to be induced by Th2 cytokines and control M2 activation [122,132]. Mice with myeloid-specific deletion of PPARδ or PPARγ show increased M1 and decreased M2 markers in WAT and liver and develop systemic insulin resistance [122,132–135]. The M1/M2 paradigm is also relevant in Kupffer cells in the liver. Myeloid PPARδ deletion worsens hepatic steatosis in mice fed on a high-fat diet [122,135]. It has been shown that macrophages from these mice produce factors that promote adipocyte and hepatocyte dysfunction in vitro [122]. Earlier studies also demonstrated an anti-inflammatory role for PPARs and LXRs, which correlates
well with the atheroprotective roles for these nuclear receptors [136–138].

GPCRs (G-protein-coupled receptors)

Although saturated fatty acids are known to induce inflammatory signalling pathways, epidemiological studies show that Mediterranean diets high in polyunsaturated ω−3 (n−3) fatty acids actually reduce the incidence of metabolic diseases [139–142]. ω−3 fatty acid derivatives, such as DHA (docosahexaenoic acid), EPA (eicosapentaenoic acid) and resolvins, exhibit anti-inflammatory activities [143]. DHA and EPA have been shown to bind to the GPCR GPR120 on macrophage surfaces. GPR120 ligation inhibits the actions of TNFα and reverses insulin resistance brought on by a high-fat diet [144]. GPR120 and PPARs share several fatty acid ligands, suggesting potential cross-talk between these two signalling pathways [145].

CONCLUDING REMARKS

The host immune system is essential for defending against foreign pathogens. Macrophages rely on the rapid influx of extracellular glucose for ATP production via anaerobic respiration [146–148]. As such, the ability of pathogen-stimulated macrophages to inhibit glucose uptake and insulin sensitivity in other metabolically demanding tissues is thought to be a mechanism by which immune cells sequester energy stores for defence [149–151]. However, in states of gluttony and energy storage, these evolutionary pathways have become detrimental. As the metabolic syndrome is a rapidly rising global epidemic affecting ∼8% of the U.S. population alone and over 170 million people worldwide, efforts to identify effective therapies for treatment of associated pathologies are paramount [ADA (American Diabetes Association), WHO (World Health Organization)]. Exercise and healthy diets are most effective in improving the outcome of the metabolic syndrome [152,153]. However, lifestyle changes are often an unachievable ideal for many patients, and therefore development of medications is crucial. Growing evidence indicates that macrophage activation plays a key role in metabolic dysregulation. Understanding the contribution of macrophages to disease pathogenesis can help in the development of immunometabolic therapeutics to treat metabolic diseases.

As described above, macrophages have evolved to sense dietary fats. The role of cholesterol in macrophage pro-inflammatory responses and atherosclerosis is well established. Studies have demonstrated further that fatty acids have a broad spectrum of activity on macrophage activation [77–79,144]. This is particularly relevant in obesity, in which the interaction of adipocyte and macrophage through fatty-acid-dependent mechanisms is critical to metabolic homeostasis (Figure 3). Dietary ω−3 fatty acids and their derivatives, including EPA, DHA and resolvins, can inhibit inflammatory responses through GPCRs or PPARs [143,144] and, as such, represent an attractive means for dietary intervention to reduce metabolic inflammation. In addition to dietary fats, studies have suggested that some amino acids, such as arginine and glutamine, promote insulin sensitivity and insulin secretion. However, epidemiological data also suggest that levels of branched-chain amino acids are associated with diabetes as early as 12 years before the onset of frank insulin resistance [154,155]. The role of amino-acid-sensing pathways in macrophage function and metabolic inflammation is currently unclear. In cultured macrophages, glutamine and arginine are critical for cytokine secretion, eicosanoid production and phagocytic uptake during macrophage activation [156]. mTOR (mammalian target of rapamycin), a major amino-acid-sensing molecule, is anti-inflammatory in the macrophage. However, mTOR inhibition by rapamycin blocks MCP-1 production, despite its pro-inflammatory phenotype [157]. Additional work is needed to clarify the roles of amino acids in metabolic syndrome and whether these effects are mediated, in part, through macrophage activation.

Although it is evident that metabolic stress (e.g. fatty acids, ceramides and oxLDL/cholesterol) induces macrophage inflammation, the detailed mechanisms through which pro-inflammatory signalling pathways cause metabolic diseases, notably in the setting of insulin resistance, remain unclear. For example, contradictory results have challenged the role of myeloid JNK1 in insulin resistance [158,159]. It appears that the initiation of a chronic inflammatory cycle may be due to loss of anti-inflammatory and/or regulatory signalling. However, the beneficial effects associated with alternative activation also require further investigation, as Th2 cytokines are known to mediate allergic responses. Recent studies have implicated several other immune cell types, such as T-lymphocytes, mast cells, natural killer cells and eosinophils, in the modulation of insulin sensitivity [124,160–165]. For example, T-cell-deficient Rag−/− (recombination-activating gene) mice are more susceptible to diet-induced obesity and adoptive transfer of CD4+ Foxp3+ (forkhead box P3) regulatory T-cells restores energy balance in these mice [160,165,166]. These studies indicate that the interactions between innate and adaptive immune systems also contribute to the onset of the metabolic syndrome and implicate an autoimmune response in the associated pathologies. What have not been described are the temporal recruitment and activation of various immune cells in metabolic tissues and the role of their interaction in metabolic diseases.

Other anti-inflammatory or immunomodulatory mechanisms may be relevant in metabolic homeostasis. Certain miRNAs (microRNAs) are up-regulated by TLR signalling and act through NF-κB pathways to dampen the inflammatory response [167,168]. miRNAs have also been implicated in atherosclerotic plaque initiation and expansion [169]. In addition, gut flora has been shown to modulate energy-utilization efficiency and adiposity and contribute to the onset of metabolic diseases [170,171]. Helminth infection is known to deactivate the immune response, and mice infected with parasitic worms exhibit improved insulin sensitivity, suggesting the potential use of helminthic antigens for therapies. Lastly, exercise reduces blood inflammatory markers and improves metabolic parameters. The so-called myokines produced by muscle after physical activity may modulate macrophage activation [172–175]. In fact, exercise-induced improvements in the inflammatory profile were found to be independent of weight loss [176,177]. Through understanding these different aspects of metabolic-related immune responses, it may be possible to design drugs to specifically target the feedforward loop of metabolic-stress-induced inflammation without unwanted side effects, such as immunosuppression or allergic responses.

ACKNOWLEDGEMENT

We thank K. Stanya for valuable comments.

FUNDING

P.B. is supported by the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) (training grant number T90DK070078). C.H.L. is supported by the American Diabetes Association, the American Heart Association and the National Institutes of Health (grant number R01DK075046).
Myoishi, M., Hao, H., Minamino, T., Watanabe, K., Nishihira, K., Hatakeyama, K., Asada,
Han, S., Liang, C. P., DeVries-Seimon, T., Ranalletta, M., Welch, C. L., Collins-Fletcher,
Peyssonnaux, C., Datta, V., Cramer, T., Doedens, A., Theodorakis, E. A., Gallo, R. L.,
Parathath, S., Mick, S. L., Feig, J. E., Joaquin, V., Grauer, L., Habiel, D. M., Gassmann,
Bedossa, P., Clement, K. and Pepin, J. L. (2011) Chronic intermittent hypoxia is a major
cause of non-alcoholic fatty liver disease. J. Hepatol. 56, 1670–1677.

120 Yashodhara, B. M., Umakanth, S., Pappachan, J. M., Bhat, S. K., Kamath, R. and Choo,
ser, A., Kojima, O., Aoyama, H., Nakagawa, Y., Figura, C., Inoue, T., Bao, Y. et al. (2008) Lack of interleukin-1 receptor I (IL-1R) protects mice from high-fat diet-induced adipose tissue inflammation coincided with improved glucose homeostasis. Diabetes 57, 1688–1698


130 Vats, D., Mukundan, L., Odegaard, J. I., Zhang, L., Smith, K. L., Morel, C. R., Wagner,

131 Lee, C. H., Kang, K., Mehrl, I. R., Nofsinger, R., Alaynick, W. A., Chong, L. W., Rosenfeld,

132 Odegaard, J. I., Ricardo-Gonzalez, R. R., Golofth, M. H., Morel, C. R., Subramanian,

133 Bouhlel, M. A., Derudas, B., Rigamonti, E., Dievart, R., Brozek, J., Haulon, S., Zawadzki,


135 Odegaard, J. I., Ricardo-Gonzalez, R. R., Red Eagle, A., Vats, D., Morel, C. R., Golofth,


142 Yashohdara, B. M., Umakanth, S., Pappachan, J. M., Bhat, S. K., Kamath, R. and Choo,
ser, A., Kojima, O., Aoyama, H., Nakagawa, Y., Figura, C., Inoue, T., Bao, Y. et al. (2008) Lack of interleukin-1 receptor I (IL-1R) protects mice from high-fat diet-induced adipose tissue inflammation coincided with improved glucose homeostasis. Diabetes 57, 1688–1698
