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Inflammation and metabolic disorders

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Metabolic and immune systems are among the most fundamental requirements for survival. Many metabolic and immune response pathways or nutrient- and pathogen-sensing systems have been evolutionarily conserved throughout species. As a result, immune response and metabolic regulation are highly integrated and the proper function of each is dependent on the other. This interface can be viewed as a central homeostatic mechanism, dysfunction of which can lead to a cluster of chronic metabolic disorders, particularly obesity, type 2 diabetes and cardiovascular disease. Collectively, these diseases constitute the greatest current threat to global human health and welfare.

The incidence of obesity worldwide has increased drastically during recent decades. Consequently, obesity and associated disorders now constitute a serious threat to the current and future health of all populations on Earth. The World Health Organization estimates that more than 1 billion adults worldwide are overweight, 300 million of whom are clinically obese — defined as having a body mass index equal to or greater than 30 kg m^{-2} (ref. 1). Particularly alarming is the equally marked increase in obesity among children[2]. Obesity is associated with an array of additional heath problems, including increased risk of insulin resistance, type 2 diabetes, fatty liver disease, atherosclerosis, degenerative disorders including dementia, airway disease and some cancers[3] (Fig. 1). This cluster of pathologies has also started to emerge in children at young ages, a phenomenon that was inconceivable only a few decades ago.

This article focuses on obesity and type 2 diabetes, illustrating the links between nutrient- and pathogen-sensing pathways, and the interfacing of metabolic and inflammatory responses through these links as the mechanistic core of chronic and common metabolic diseases.

Key conceptual considerations

During the past decade, it became clear that inflammation is a key feature of obesity and type 2 diabetes[4]. Before delving into the mechanisms underlying metabolic dysfunction and the connections to inflammation, insulin action and metabolic disease clusters, it would be helpful to explore these terms and perhaps introduce a few crucial concepts that might differ from the classical context in which these terms have already been used and interpreted. Without venturing into the complexities of nomenclature, it would be useful to mention, at the onset of this discussion, that both 'inflammation' and 'metabolic syndrome' need to be redefined. This is essential to exploring the question of causality between the state of inflammation and the components that make up the cluster of metabolic pathologies (traditionally referred to as metabolic syndrome increasing metabolic disease risk)[3] and therefore to developing effective mechanistic models and, ultimately, therapeutic strategies. For the purposes of this review, I occasionally refer to metabolic syndrome as a cluster of chronic and complex diseases all of which feature metabolic deterioration as at least one component.

With regard to inflammation, the traditional features of this state do not apply to the diseases in question. In the classic literature, inflammation is described as the principal response of the body invoked to deal with injuries, the hallmarks of which include swelling, redness, pain and fever (tumor, rubor, dolor and calor)[5]. This often short-term adaptive response is a crucial component of tissue repair and involves integration of many complex signals in distinct cells and organs. However, the long-term consequences of prolonged inflammation are often not beneficial. This certainly seems to be the case in metabolic diseases. Although many of the same mediators are involved in obesity and diabetes, few, if any, of the classic features of inflammation have been observed. Therefore, it would be useful to set out a distinct form of injury response or subclass of inflammation — sometimes referred to as 'low-grade' or 'chronic' — or to describe an altogether separate state with a new term, perhaps 'meta-flammation' (metabolically triggered inflammation). This condition is principally triggered by nutrients and metabolic surplus, and engages a similar set of molecules and signalling pathways to those involved in classical inflammation.

Evolutionary perspectives

Why are metabolic diseases so common and why are they so crucially linked to inflammatory processes? Perhaps we can gain insight through the fundamental biological design of an organism. Among the most critical processes to species survival are the ability to withstand starvation and the capacity to mount an effective immune response to pathogens. The former selects for energy efficiency and favours the storage of excess calories when access to food is intermittent. However, in the presence of a continuous nutritional surplus, this once advantageous metabolic state could set the stage for excess adiposity and its associated

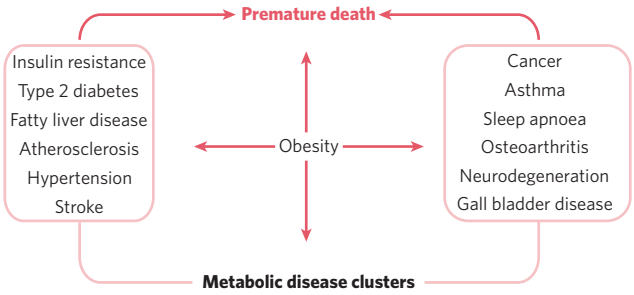

Figure 1 | Clustering of metabolic diseases. Obesity is considered to be a central feature that increases the risk for a vast array of diseases, with significant morbidity and mortality. In general, the mechanistic basis of the link between obesity and the diseases listed on the right is poorly understood compared with that of those listed on the left.

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problems. The ability to fight off an infection has also led to selection of strong immune responses, particularly after massive population declines during periods of infectious disease epidemics and pandemics[6,7]. The combination of these traits is likely to have given rise to a biological organization that is highly capable of processing and storing energy and is also equipped with a powerful, and perhaps at times overly sensitive, immune response.

There is also an intimate relationship between the immune and metabolic response systems that has many evolutionary underpinnings. First, the functional units that control key metabolic and immune functions in higher organisms have evolved from common ancestral structures. One such structure is the *Drosophila* fat body, which incorporates the mammalian homologues of the liver and the haematopoietic and immune systems[8,9] (Fig. 2). Interestingly, this site is also recognized as the equivalent of mammalian adipose tissue, sharing similar developmental and functional pathways[10,11]. The fly's fat body carries out a crucial function in sensing energy and nutrient availability, and coordinates the appropriate metabolic and survival responses[8]. It is also the site of coordination of pathogen responses with metabolic status. In higher organisms, the adipose tissue, liver and haematopoietic system have specialized into distinct functional units or organs. However, these organs have maintained their developmental heritage, which was shared in earlier organisms. Therefore, it is possible to imagine a situation in which common or overlapping pathways regulate both metabolic and immune functions through common key regulatory molecules and signalling systems. This might allow nutrients to act through pathogen-sensing systems such as Toll-like receptors (TLRs), giving rise to metabolically or nutritionally induced inflammatory responses[6,8,12,13].

It is interesting to note that both adipose tissue and the liver have an architectural organization in which metabolic cells (adipocytes or hepatocytes) are in close proximity to immune cells (Kupffer cells or macrophages) and both have immediate access to a vast network of blood vessels (Fig. 3). With this configuration, both tissues form a suitable environment for continuous and dynamic interactions between immune and metabolic responses and establish communications with other sites such as pancreatic islets and muscle (Fig. 3). In fact, this interface might contribute to the emerging importance of these two organs in the initiation and development of metabolic diseases, particularly in the context of obesity and type 2 diabetes[4,14].

A closely linked configuration and coordinated regulation of metabolic and immune responses is likely to be advantageous in certain conditions, because an organism would need to organize and redistribute its energy resources during the mounting of an immune or inflammatory response. In fact, the most primitive response systems integrate the pathogen- and nutrient-sensing pathways such that nutrients can induce immune responses and pathogens can evoke and regulate metabolic responses[6,8,15]. In this setting, we can foresee potential benefits to the activation of inflammatory or stress responses to block major anabolic signalling pathways such as the insulin/insulin growth factor (IGF) pathway. Blocking insulin signalling would divert energy sources from synthetic pathways. In this case, one might speculate that almost all stress and inflammatory signalling needs to coordinate with insulin-receptor signalling, and that all of these stress- and immune-response pathways are potentially involved in the disturbance of insulin action. However, none of these systems have evolved and adapted to be beneficial in the presence of continuous nutrient surplus such as we are now experiencing.

Taking all the evidence together, it is safe to suggest that the link between inflammatory and metabolic signalling is a delicate balance. Although there are short-term compensatory and adaptive measures to keep this delicate balance in check, the outcome is often detrimental when one arm overwhelms the other in the long term. For example, sustained exposure to pathogens or pathogen-associated components can disrupt systemic metabolic function from flies to humans[15,16]. Similarly, chronic disturbance of metabolic homeostasis, such as occurs in malnutrition or overnutrition, could lead to aberrant immune responses[4]. The current nutritional habits and lifestyles of most modern humans heavily favours metabolic overload with diminishing physical activity. Under such conditions, these historically advantageous traits and the juxtaposition of nutrient and pathogen responses have established the groundwork for chronic metabolic diseases to emerge and spread around the globe at an alarming pace. If this is the case, it is conceivable that prevention or treatment might be provided by targeting the same interface from which the metabolic disease clusters originate.

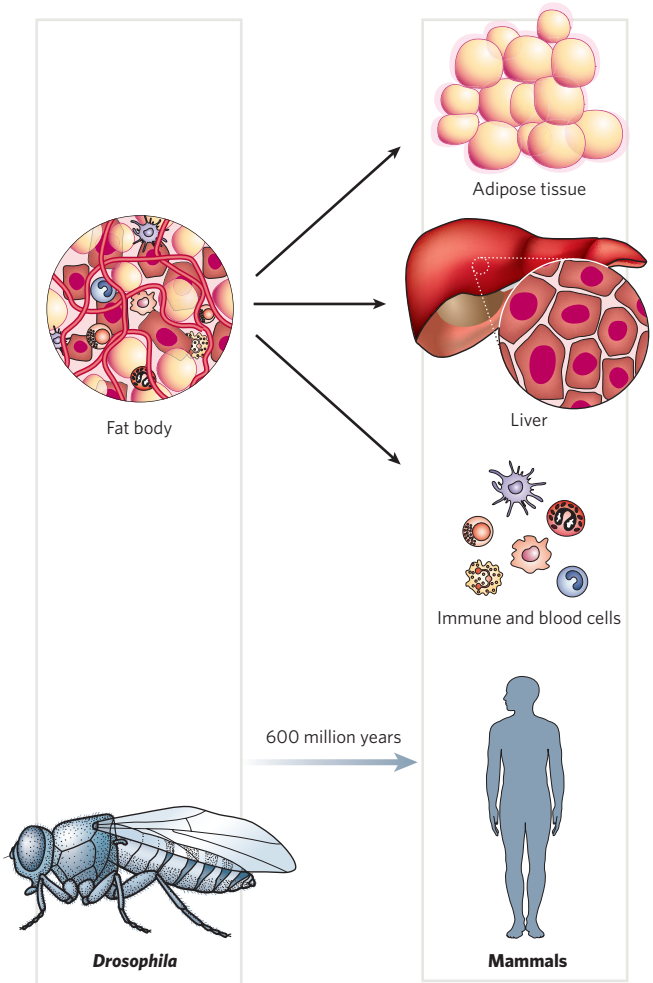

Figure 2 | Evolution of adipose tissue, the liver and the haematopoietic system into distinct organs in mammals. The adipose tissue, liver and haematopoietic system are all organized in one functional unit in *Drosophila melanogaster*, known as the 'fat body'. This developmental heritage may underlie the highly overlapping biological repertoire of these organs, their effects on metabolic and immune cells, and the close link between immune and metabolic response systems.

Obesity, inflammation and metabolic syndrome

Obesity, insulin resistance and type 2 diabetes are closely associated with chronic 'inflammation' characterized by abnormal cytokine production, increased acute-phase reactants and other mediators, and activation of a network of inflammatory signalling pathways[4]. Unequivocal experimental, epidemiological and clinical evidence produced during the past decade causally links inflammation, or the molecules and networks integral to inflammatory responses, to the development of these metabolic diseases and/or the complications that emerge from these pathologies, particularly in the context of obesity and type 2 diabetes[4,14,17].

The finding a little over a decade ago that tumour necrosis factor-α (TNF-α) is overexpressed in the adipose tissue of obese mice provided the first clear link between obesity, diabetes and chronic inflammation[18].

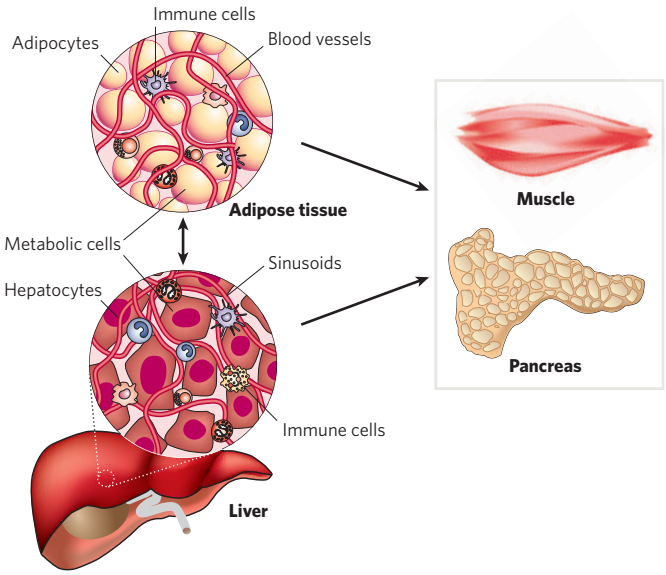

Figure 3 | Architectural organization and proximity of principal metabolic (adipocyte and hepatocyte) and immune (macrophages, Kupffer cells, lymphocytes and dendritic cells) cells in adipose tissue and liver. This configuration allows close interaction between these important cell groups and access to blood vessels for soluble mediators that communicate with other organs, including, but not limited to, skeletal muscle and the pancreas. This network is detrimental when inflammation is heightened, as in adipose tissue and/or the liver in individuals with obesity and/or type 2 diabetes.

TNF-α is a proinflammatory cytokine that activates various signal transduction cascades, including many of the pathways that are discussed below as critical inhibitors of insulin action. In obese mouse models a lack of TNF-α function results in improved insulin sensitivity and glucose homeostasis, confirming that this inflammatory response has a critical role in the regulation of insulin action in obesity[19,20]. TNF-α is also overexpressed in the adipose and muscle tissues of obese humans, and when administered exogenously leads to insulin resistance[21–24]. Whether TNF-α alone is involved in human insulin resistance has not yet been adequately addressed because of the limited power and scope of the early studies, which did not yield a detectable benefit of TNF-α neutralization[25]. Interestingly, however, the widespread use of anti-TNF-α treatments in inflammatory diseases such as rheumatoid arthritis have produced clear secondary results supporting a role for TNF-α in systemic insulin sensitivity in humans[26,27].

It is clear from studies published during the past decade that, in addition to TNF-α, various other inflammatory mediators and cytokines are also overexpressed in adipose and other tissues in experimental mouse models of obesity and in humans[4], and the measurable contribution of each inflammatory mediator is, at best, partial, even in experimental models. As cytokines and chemokines work in networks, the effect of individual molecules on metabolic function depends on their place in the hierarchy of the network; those more potent and proximal, such as TNF-α, have greater effects. The combinatorial and additive action of cytokines in metabolic homeostasis is a crucial but poorly addressed area.

Adipose tissue and immune response

The inflammatory response that emerges in the presence of obesity seems to be triggered by and to reside predominantly in adipose tissue, although other metabolically critical sites, particularly the liver, might also be involved during the course of the disease[4,14]. Recent studies have documented the unusual properties of adipocytes and centrally placed adipose tissue as a crucial site in the generation of inflammatory responses and mediators. In addition to the inherent properties of fat cells in energy management and metabolic homeostasis, adipose tissue serves as a key site for the interaction of adipocytes with other effectors of the immune system (Fig. 3).

There are also striking commonalities between adipocytes and a diverse set of immune cells (including T cells, macrophages and dendritic cells). These features are extensive and range from complement activation and production of inflammatory mediators to pathogen sensing and phagocytic properties[4,14]. Thus, a potential window through which to explore the link between metabolism and inflammation might lie at the functional interface of cells of primarily immune or metabolic nature, such as adipocytes and macrophages, and the shared response systems. Although adipose tissue is presented here as an example of functional organization and structural proximity of metabolic and immune cells, a similar argument could be made for other metabolically critical organs, particularly the liver (Fig. 3).

An important feature of inflammation is infiltration of inflamed tissues by immune cells such as neutrophils, eosinophils and macrophages. Macrophage infiltration of adipose tissue has recently been described in obese conditions in both mice and humans[28,29]. It has been suggested that expanding adipocytes or neighboring pre-adipocytes might begin to produce chemotactic signals leading to macrophage recruitment[4]. Careful examination of the morphology of adipose tissue during obesity has illustrated the convergence of macrophages on necrotic adipocytes and suggested that their presence in adipose tissue might be predominantly for clearance purposes[30]. The death of adipocytes might be a primary event enhanced by obesity, or secondary to inflammation and macrophage infiltration. Thus, it might reflect an attempt to limit the expansion of these cells.

Although it is likely that macrophage infiltration into adipose tissue makes some contribution to the emergence and maintenance of obesity-induced inflammatory responses, the extent of this and the functional involvement of macrophages in systemic metabolism are unclear. Genetic manipulation of IKK-β (inhibitor of nuclear factor-κB (NF-κB) kinase-β) signalling in myeloid lineage can affect systemic metabolic regulation[31], supporting the involvement of macrophages and/or neutrophils in insulin action. The potential participation of other immune cells such as lymphocytes remains unclear. Interestingly, disruption of insulin action in the myeloid cells does not seem to alter systemic glucose or lipid metabolism, although this question has only been addressed in atherosclerotic models[32,33]. Additional pathways at the interface between macrophage and adipocyte function in metabolic diseases are further discussed in the context of lipid signals below. However, the understanding of interactions between immune and metabolic cells is incomplete.

Lipids in inflammation and insulin resistance

Metabolic, inflammatory and innate immune processes are also coordinately regulated by lipids[34]. Several transcription factors, particularly those in the peroxisome-proliferator activated receptor (PPAR) and liver X receptor (LXR) families, seem to be crucial for modulating the intersection of these pathways. Activation of these transcription factors inhibits the expression of several genes involved in inflammatory response in macrophages and adipocytes[35,36].

Ligands to all three PPAR family members suppress production of proinflammatory cytokines, mostly through suppression of NF-κB[35,36]. Notably, unliganded PPAR-δ seems to have inflammatory functions, mediated at least in part through its association with the transcriptional repressor BCL-6 (ref. 37). Like the PPARs, LXR suppresses production of inflammatory mediators in a manner reciprocal to its regulation of lipid metabolism[38]. Signalling from TLRs inhibits LXR activity in macrophages, causing enhanced cholesterol accumulation in macrophages and accounting, at least in part, for the pro-atherogenic effects of infection[39]. Most intriguingly, TLRs are present in adipocytes and can be directly activated by nutrients, particularly fatty acids[12,13,40]. Finally, there are critical interactions between different classes of nuclear hormone receptor that might represent a critical component of the anti-inflammatory actions of these molecules[41,42].

Another group of molecules that coordinates lipid responses in adipocytes and macrophages and that is linked to the pathways described

above is the lipid chaperone proteins. Animals lacking the adipocyte/macrophage fatty-acid-binding proteins (FABPs) aP2 and MAL1 exhibit a phenotype akin to that of mice and humans treated with PPARγ ligands, indicating that FABPs and PPARs might act on similar pathways in controlling the biological effects of lipids[43,44]. Inflammatory pathways, including the activation of c-Jun amino-terminal kinase (JNK) and IKK, and insulin action in target cells are also strongly influenced by these FABPs. Mice lacking aP2 and MAL1 are protected against almost every aspect of metabolic syndrome, including visceral obesity, insulin resistance, hepatosteatosis and atherosclerosis[43,45,46]. Interestingly, a rare loss-of-function genetic variant at the aP2 locus produces a very similar protective phenotype in humans[47]. Most recently, resistance to asthma was also demonstrated in aP2-deficient mice, establishing the first potential link between metabolic regulation and airway inflammation[48]. Although our understanding of the precise mechanisms that underlie FABP action is incomplete, it is clear that their absence is both anti-inflammatory and protective of metabolic function during nutrient overload[49]. FABPs also modulate lipid composition and fluxes, a critical feature of their biological function. In fact, it seems that location in the body is a crucial factor for determining whether lipids promote or suppress inflammation and insulin resistance. Even elevated plasma lipid levels might not be inflammatory alone, but instead might be correlated with the extent of stimulation of inflammatory pathways, because the hyperlipidaemic state is indicative of redistribution of lipids from adipose tissue to muscles and the liver.

Inflammatory signalling and insulin action

How do inflammatory signals disrupt insulin action and mediate insulin resistance in obesity? The insulin signalling pathway is not presented here in detail because of space limitations, and readers are referred to excellent recent reviews[50,51]. However, to summarize briefly, insulin and IGF receptors belong to a receptor tyrosine kinase family and, unlike other receptors in this family, use docking proteins to mediate their signalling. Among a large number of intracellular substrates used by these receptors, six belong to the family of insulin receptor substrate (IRS) proteins (IRS-1–6)[50,51]. Insulin stimulates tyrosine phosphorylation of IRS proteins, which is a crucial event in mediating insulin action. This step in insulin-receptor signalling is defective in most cases of systemic insulin resistance, both in experimental models and in humans[4]. TNF-α also targets this element of insulin-receptor signalling through inhibitory serine phosphorylation of IRS-1 (ref. 52). As this post-translational modification of IRS-1 through serine phosphorylation has also been detected in insulin-resistant cells and tissues in mice and humans, elucidation of the mechanisms that lead to phosphorylation of IRS-1 and other substrates has became a major focus in many laboratories in recent years.

It has now been established that IRS-1 is phosphorylated at serine residues by various kinases that interfere with the ability of this protein to engage in insulin-receptor signalling and result in alterations in insulin action[50,53,54] (Fig. 4). In addition, suppressor of cytokine signalling (SOCS) proteins seem to inhibit insulin action at the level of insulin-receptor substrates, although through a different mechanism[55–57].

Among these IRS-modifying enzymes, mounting evidence indicates that activation of JNK, IKK and conventional protein kinase C (PKC) is central to mediating insulin resistance in response to various stresses that occur in obesity and other conditions of insulin resistance (Fig. 4). They have all been reported to be able to inhibit insulin action by serine phosphorylation of IRS-1 (refs 53, 58, 59), although the activity of IKK in this regard has not yet been well established under physiological conditions. IRS-1 serine phosphorylation disrupts insulin-receptor signalling through several distinct mechanisms and blocks insulin action[60,61]. These kinases also exert powerful effects on gene expression, including promoting further inflammatory gene expression through activation of activator protein-1 (AP-1) complexes and NF-κB[62]. However, this aspect has not yet been thoroughly explored in metabolic homeostasis.

Most importantly, in obesity there is a striking increase in JNK activity in critical metabolic sites such as adipose and liver tissues[63] as well as in the hypothalamus[64]. JNK is activated upon exposure to cytokines such as TNF-α, as well as by free fatty acids and internal cues such as endoplasmic reticulum stress, all of which might underlie the obesity-induced activity[4,53,65]. Genetic JNK1-deficiency protects mice from obesity-induced JNK activation, IRS-1 serine phosphorylation, and, consequently, insulin resistance, fatty liver and diabetes[63,66]. Recent studies examining the functional interactions between JNK isoforms revealed that JNK2 also participates in metabolic regulation but that this function is normally masked owing to compensation by JNK1 (ref. 66). JNK2 activity has also been implicated in the pathogenesis of atherosclerosis[67]. It is not yet clear whether these pathological states are exclusive to the aberrant action of individual JNK isoforms or a function of total JNK activity in specific target tissues. Regardless of this uncertainty, interventions to block JNK activity in established models of obesity and diabetes improved systemic glucose homeostasis and insulin sensitivity, as well as atherosclerosis, suggesting that JNK inhibition might be a promising therapeutic avenue for diabetes[67–69].

Another inflammatory kinase that is critical in the development of insulin resistance and metabolic dysfunction is IKK-β. Mice that are heterozygous for a null mutation in IKK-β are partly protected from obesity-induced insulin resistance, and inhibition of IKK-β by administration of high-dose salicylates improves insulin action in experimental models and humans[70,71]. Studies involving tissue- or cell-type specific modulation of IKK-β reveal that its activity in the liver affects systemic metabolism; however, its role in muscles is probably less important in terms of metabolic regulation[72]. Similarly to JNK, experimental activation of this kinase in the liver seems to be sufficient to generate systemic insulin resistance[72]. Interestingly, myeloid-specific deletion of IKK-β results in partial protection against obesity- or lipopolysaccharide-induced insulin resistance, providing clear evidence that IKK-β activity in myeloid cells can participate in the regulation of systemic metabolic homeostasis[31].

Protein kinase C is also important in interaction between the inflammatory and metabolic pathways, and in particular has been implicated as a kinase downstream of lipid signals[34,73,74]. Fatty acid metabolites such as

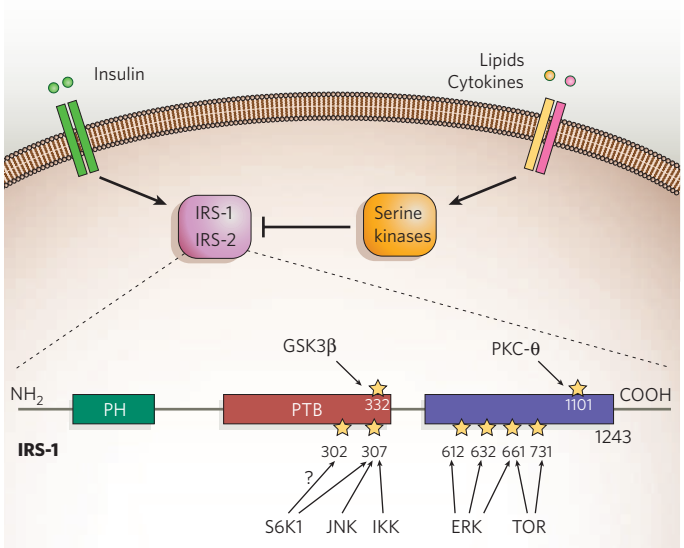

Figure 4 | Insulin-receptor signalling interfaces with inflammatory signalling at the level of insulin-receptor substrates through activation of serine kinases. These kinases respond to both lipids and cytokines. Both IRS-1 and IRS-2 contain a number of serine residues (indicated by white stars) that are targeted by various kinases, which have been more extensively mapped for IRS-1 (ref. 50). All of the molecules listed that regulate insulin action in response to inflammatory signals converge on IRS-1. Many serine phosphorylation sites also seem to exist in IRS-2 but have not yet been characterized in detail. ERK, extracellular regulated mitogen-activated protein kinase; GSK3β, glycogen synthase kinase 3β; PH, pleckstrin homology; PTB, phosphotyrosine binding; S6K1, ribosomal protein S6 kinase polymerase 1; TOR, target of rapamycin.

fatty acyl coenzyme As and diacylglycerides can activate PKC-θ in muscles or PKC-δ in the liver and inhibit insulin action[34,74]. Mice deficient in PKC-θ are protected against fatty-acid-induced insulin resistance, confirming the contribution of this kinase to metabolic regulation *in vivo*[73]. At the mechanistic level, PKC-θ is known to activate IKK and might contribute to insulin resistance through this pathway. Interestingly, interactions also occur between PKC, JNK and IKK, although these have not been tested in the context of metabolic homeostasis[75]. Characterization of the isoforms of these kinases involved in disrupting insulin action among different species, especially humans, is a critical issue that has so far been addressed only in part.

Endoplasmic reticulum stress in obesity and type 2 diabetes

A fundamental issue that is not yet well understood is why inflammation develops in obesity. What stresses initially cause the activation of inflammatory pathways? Are these signalling pathways emerging from a common mechanistic platform and integrating with each other? Recent data from experimental models indicate that endoplasmic reticulum (ER) stress is critical to the initiation and integration of pathways of inflammation and insulin action in obesity and type 2 diabetes.

The ER is a vast network of membranes in which all the secretory and membrane proteins are assembled into their secondary and tertiary structures. Proper folding, maturation, storage and transport of these proteins take place in this organelle. Unfolded or misfolded proteins are detected, removed from the ER and degraded by the 26S proteasome system[76,77]. Accumulation of unfolded proteins, energy and nutrient fluctuations, hypoxia, toxins, viral infections and increased demand on the synthetic machinery give rise to perturbations in the ER lumen and create stress. Under these conditions, the ER activates a complex response system known as the unfolded protein response (UPR) to restore the functional integrity of the organelle[76,77]. The principal branches of UPR signalling are mediated through three molecules: inositol-requiring enzyme 1 (IRE-1), PKR-like endoplasmic-reticulum kinase (PERK) and activating transcription factor 6 (ATF6)[78,79].

Notably, the two principal inflammatory pathways that disrupt insulin action, JNK–AP-1 and IKK–NF-κB, are linked to IRE-1 and PERK activity during ER stress[80–82]. IRE-1 is linked to activation of JNK through a pathway involving TNF-receptor-associated factor 2 (ref. 80). Activation of both IRE-1 and PERK is also linked to the IKK–NF-κB pathway, although through distinct mechanisms. Whereas IRE-1 interacts with IKK-β through TNF-receptor-activated factor 2 (TRAF2), PERK activation leads to degradation of IκB and therefore facilitates the activity of NF-κB[81,82].

So, we can postulate that the ER might be a site for the sensing of metabolic stress and the translation of that stress into inflammatory signalling and responses. In fact, the ER could be considered an essential and ancient site of integration between nutrient and pathogen responses as it is very sensitive to glucose and energy availability, lipids, pathogens and pathogen-associated components. In addition to increased demand on the synthetic capacity of several organs such as the liver and adipose tissue, increased adiposity in obesity produces an environment that further challenges ER function and capacity owing to architectural constraints that limit ER expansion as well as altered energy and nutrient availability. So, obesity provides many conditions that could lead to ER stress.

Work in our laboratory has recently demonstrated that in both dietary and genetic obesity ER stress is increased in adipose and liver tissues[65]. In cellular systems, the induction of ER stress leads to insulin resistance, at least in part through IRE-1-dependent activation of JNK. Modulation of ER-folding capacity through gain- and loss-of-function studies with X-box binding protein (XBP-1) showed a close link between ER function and insulin action *in vitro* and *in vivo*[65]. These initial observations were followed by independent studies that linked ER function to insulin sensitivity[83,84]. Together, these results indicate that ER stress has an important role in mediating insulin resistance in obesity in animal models and that increasing cellular folding capacity might be a promising therapeutic approach, if this concept is applicable to humans. Indeed, recent studies have demonstrated that orally active small-molecule chemical chaperones are extremely effective in alleviating obesity-induced ER stress and JNK activation, and in treating insulin resistance and type 2 diabetes in mice[85].

ER stress also provides several links with the emergence of inflammatory responses. First, and as stated above, ER stress leads to activation of both JNK and IKK[80–82]. Second, inflammatory mediators can trigger ER stress and lead to propagation of general stress responses[86]. Third, ER stress leads to activation of CREB-H, which may have an important role in inflammatory and acute-phase responses in the liver[86]. Fourth, the ER is a major source of reactive oxygen species (ROS), and, consequently, oxidative stress in all cells[87,88]. Oxidative stress is emerging as a feature of obesity and an important factor in the development of insulin resistance in obesity[89–91].

In metabolic disease, the molecular outcomes of oxidative stress have been most clearly linked to diabetic complications through endothelial cell dysfunction[92]. However, recent evidence indicates that oxidative stress and mitochondrial dysfunction also have important roles in type 2 diabetes[89–91,93]. These pathways are also coupled to activation of inflammatory pathways and insulin resistance in adipocytes and muscle cells, and impaired insulin secretion in pancreatic β-cells[89–91]. Both the NF-κB and JNK pathways can be activated under conditions of oxidative stress, and this may be important for the ability of ROS to mediate insulin resistance. Taken together, the effector arms of ER stress and the associated stress responses are tightly linked to inflammatory pathways at many levels that are crucial for insulin action and metabolic homeostasis.

Space limitations preclude detailing the implications of the mechanisms discussed here for islet function and survival. However, all of the pathways that act at the interface of metabolic and inflammatory

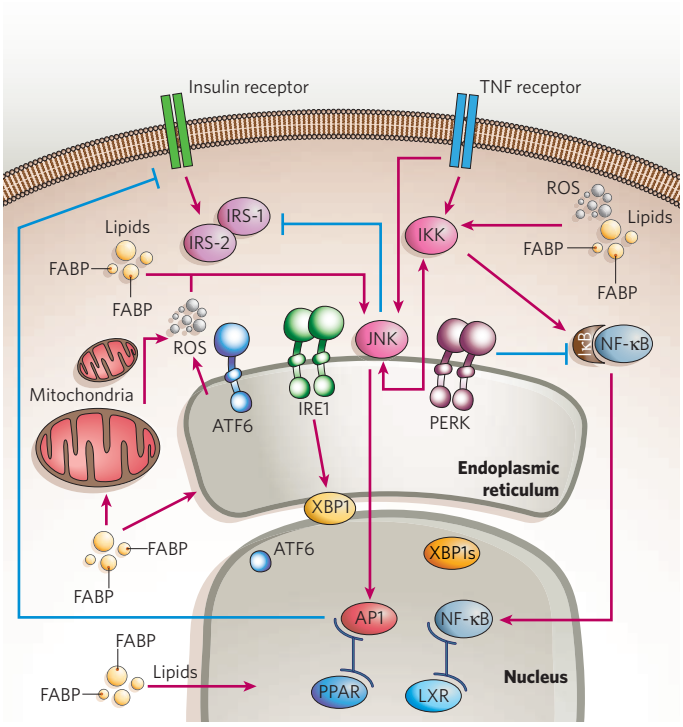

Figure 5 | Molecular pathways integrating stress and inflammatory responses with insulin action. IRS-1 and 2 are crucial signalling molecules in insulin action. Activation of JNK by cytokine signalling, lipid products, ROS or through IRE1 during ER stress leads to serine phosphorylation of IRS-1 and 2, and consequently inhibits insulin signalling. Similar signals, including PERK, also activate IKK and inhibition of insulin action through a series of transcriptional events mediated by NF-κB. JNK also regulates transcription through AP-1. Lipid-activated transcriptional events are mediated by nuclear hormone receptors PPAR and LXR. The biological activities of lipids are regulated by FABPs that function as chaperones. Mitochondria and the ER can both contribute to ROS production. ATF6 and XBP1 are critical regulators of ER function and its adaptive responses.

responses have critical direct and/or indirect effects on β-cells. This is particularly true in ER stress and related signalling pathways[76,77]. Hence, these mechanisms have great potential to underscore the integrated pathophysiology of type 2 diabetes characterized by both insulin resistance and defective insulin secretion. Also not discussed is the action of insulin on the central nervous system (CNS) and consequences of CNS insulin resistance, not only in systemic metabolic homeostasis but also in neurodegeneration and dementia. It has even been proposed that defective insulin action in the nervous system be labelled type 3 diabetes, particularly in the context of Alzheimer's disease[94]. It is interesting to note that the mitochondrial effects of the PPAR-γ coactivator-1α (PGC-1α) have an important role in oxidative stress in both type 2 diabetes and neurodegenerative disease[93,95,96].

The chicken or egg question

There is experimental evidence clearly demonstrating that, under defined conditions, inflammatory mediators 'alone' can trigger insulin resistance in cells, experimental models and humans in the absence of other triggering factors, such as obesity. This observation, on the surface, suggests that inflammation is proximal to metabolic deterioration. Although this concept holds true for selected conditions, such as severe infections, burns and trauma, it is not clear whether the same is applicable to obesity or other chronic metabolic disorders. Furthermore, it is also clear that metabolic dysfunction can be triggered by chronic excess of nutrients, such as lipids and glucose. However, in this case, these signals also simultaneously trigger inflammatory responses. In this setting of metabolic excess, it is more likely that metabolic signal(s) are the triggers for inflammatory responses, which then further disrupt metabolic function, leading to more stress and inflammation, and so on. Such vicious cycles could be described for all of the critical events and identified mechanisms leading to further metabolic deterioration (Fig. 5).

For example, at the molecular and cellular levels, nutrients such as lipids and cytokines can trigger inflammatory kinases, such as JNK and IKK, and ER stress. The presence of ER stress, regardless of the proximal signal, can also activate JNK and IKK, both of which then regulate the production of various cytokines, including TNF-α. Notably, exposure to inflammatory cytokines such as TNF-α can induce ER stress, and ER stress itself can cause an increase in the expression of TNF-α or perhaps more general inflammatory responses[82]. A similar situation could occur for ROS, which might emerge from mitochondria and/or the ER and activate JNK and IKK. This would cause more ER stress, block insulin action and produce more ROS, which would, in turn, produce broader inflammatory responses. Some of the pathways integrating inflammation with insulin action are detailed in Fig. 5. As this scheme shows, it is possible to enter the network from an inflammatory or metabolic gateway and still end up with the same vicious loop.

Another way to look into the chicken or egg question is to ask whether inflammation can simply be a function of inefficient nutrient clearance. If this is the case, as long as the apparatus dealing with nutrient clearance is operating effectively, there should not be inflammation related to metabolic signals. Although this is certainly a valid consideration, it would require several issues to be resolved. For example, a clearance-related theory would imply that, under physiological or homeostastatic conditions, there are yet to be identified mechanisms that can prevent the engaging of inflammatory pathways during nutrient fluctuations. Furthermore, clearance must not only be efficient but must also take place in appropriate sites — for example, glucose by the muscle and fat by adipose tissue. Even if these mechanisms were present, excess nutrients could still trigger stress/inflammatory responses during their intracellular metabolism. Perhaps control at this level might involve the anti-inflammatory actions of glucocorticoids and their functional interactions with other nuclear hormone receptors responding to potential nutrient-derived signals[41,42]. Nevertheless, in an integrated homeostatic model, long-term exposure to nutrient excess is highly unlikely to be managed simply by adjusting the ability to clear and enhance metabolism at target cells. Discovery of such sensing and control paradigms might nevertheless open the way for therapeutic approaches to enhance the capacity of the endogenous machinery so that stress/inflammatory responses are prevented during exposure to the same flow of metabolic signals.

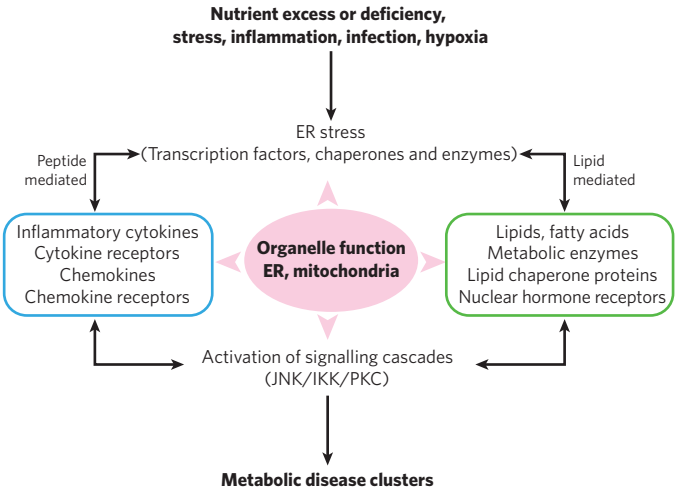

Figure 6 | Therapeutic targets at the interface between metabolic and inflammatory pathways. The pathways are divided into peptide- and lipid-mediated targets for practical purposes and do not represent an exhaustive list. Treating several loci involved in the disease process by targeting organelles such the ER and mitochondria represents a new approach to treating metabolic diseases.

Therapeutic opportunities

This article opened with the statement that metabolic and immune systems are among the most fundamental requirements for survival. How, then, can we manipulate the interface of such fundamental biological response pathways for therapeutic purposes without severe consequences to the organism? This is a formidable challenge but some promise exists and is emerging.

Some potential therapeutic avenues are summarized in Fig. 6. For practical purposes, these are divided into peptide- and lipid-mediated pathways. For peptides, the most obvious targets are cytokines, chemokines or their receptors. Although there have been some encouraging results in relation to this approach (for example anti-TNF or anti-CCR2 (chemokine (C–C motif) receptor 2) therapies), it is likely that the benefits of targeting a single cytokine or signalling receptor will be limited[4,14].

A more comprehensive approach would be to tackle a more central locus in the production of not single molecules but a network of responses. The best examples for this approach would be JNK and IKK pathways. Through inhibition of IKK, high-dose salicylates can improve glucose metabolism in both obese mice and diabetic humans[70,71,97]. It is possible that inhibition of other inflammatory kinases might have similar effects. In the preclinical setting, genetic, biochemical and pharmacological targeting of inflammatory signalling pathways improves insulin action[4]. For example, the targeting of JNK using an inhibitory peptide, synthetic small-molecule inhibitors or RNA interference (RNAi)-based technologies has been shown to improve insulin action in various mouse models[68,69]. There is also strong genetic evidence that the JNK pathway is relevant to human disease[98]. However, developing effective orally active small-molecule inhibitors of JNK that are isoform selective has been challenging. This still constitutes a bottleneck in addressing the therapeutic potential of targeting JNK in humans and needs to be addressed.

Among the lipid-related pathways, the main example of therapeutic success is the thiazolidinediones[99]. These PPARγ ligands are insulin-sensitizing compounds, in use for humans, that function by regulating lipid metabolism and exhibiting anti-inflammatory effects. FABPs can also be targeted by small molecules to inhibit both adipocyte and

macrophage function, and to treat type 2 diabetes and atherosclerosis in mice[43,46]. Although many other possible molecules could be listed, those that engage directly with lipids as ligands or signals and exhibit the dual activity on metabolic and inflammatory pathways are mentioned here.

A final and truly paradigm-shifting approach would be 'organelle therapy'. As mitochondrial defects and ER dysfunction are central to the activation of several important inflammatory pathways, chemical correction of their functional deficiency might result in new treatments to stop the vicious cycle between metabolic and inflammatory cascades and rescue insulin action and/or correct metabolic disorders. In such a case, several of the mechanisms underlying metabolic dysfunction could be treated simultaneously for superior efficacy and safety. The use of chemical chaperones in experimental models supports the feasibility of such an approach in metabolic disease, although it is not yet clear whether such concepts are applicable to human disease[85]. Recently, the possibility of targeting mitochondrial dysfunction has also been suggested[100]. In searching for new and effective therapeutics, it might be useful to use a systems-chemistry approach to modify integrated outcomes rather than targeting single molecules with the hope that the desired systematic effect might be generated. In other words, it is likely that creating a 'new homeostasis' will require the modification of more than one target. ■

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