Inflammatory Mechanisms in Obesity

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Abstract

The modern rise in obesity and its strong association with insulin resistance and type 2 diabetes have elicited interest in the underlying mechanisms of these pathologies. The discovery that obesity itself results in an inflammatory state in metabolic tissues ushered in a research field that examines the inflammatory mechanisms in obesity. Here, we summarize the unique features of this metabolic inflammatory state, termed metaflammation and defined as low-grade, chronic inflammation orchestrated by metabolic cells in response to excess nutrients and energy. We explore the effects of such inflammation in metabolic tissues including adipose, liver, muscle, pancreas, and brain and its contribution to insulin resistance and metabolic dysfunction. Another area in which many unknowns still exist is the origin or mechanism of initiation of inflammatory signaling in obesity. We discuss signals or triggers to the inflammatory response, including the possibility of endoplasmic reticulum stress as an important contributor to metaflammation. Finally, we examine anti-inflammatory therapies for their potential in the treatment of obesity-related insulin resistance and glucose intolerance.

MODERN THREAT OF METABOLIC DISEASE: THE RISE AND CONSEQUENCES OF HUMAN OBESITY

In the past 50 years, the occurrence of human obesity has risen tremendously across the globe. In the United States, obesity (defined as a body mass index greater than 30) is now prevalent in more than 30% of the adult population (1). High-income countries are not the only ones affected by obesity, as the condition is on an alarming rise in the developing world as well (2). The World Health Organization reports that at least one billion adults are overweight and 300 million are obese, and these numbers are expected to rise in the future without intervention (3). Importantly, the obesity epidemic is now also affecting children, as the prevalence of childhood obesity has tripled in the past 30 years, leading to health problems in this susceptible population (4).

Interestingly, carrying a large percentage of fat is not necessarily detrimental to an animal's health. Although obesity is rare in the wild, there are naturally obese animals, such as Svalbard reindeer, seals, and polar bears. Moreover, in these cases the high degree of adiposity does not preclude but actually contributes to their fitness, equipping them to survive in often harsh environments (5). Yet naturally occurring obesity is in contrast to the obesity found in modern humans, which is accompanied by inflammation and often by disease and disability. Although there is no clear and identifiable advantage to being obese in modern humans, it is worth noting that human obesity does not always result in disease, and therefore, the threshold for tolerable fat differs among individuals and may be determined by environmental and genetic variables.

The recent rise in human obesity is caused by increased energy intake and decreased energy expenditure that results in a massive increase in adipose tissue that is generally harmful to health. Indeed, the rise in human obesity is closely associated with an increase in diseases such as type 2 diabetes (T2D), cardiovascular disease, hepatic steatosis, airway disease, neurodegeneration, biliary disease, and certain cancers (6). These obesity-associated maladies are subsequently linked to reduced life expectancy and premature death. In fact, most of the world's population today lives in countries where individuals are more likely to die from the consequences of being overweight than underweight (3). In light of these facts and the massive burden of obesity-associated care on health-care systems, obesity and its related disease cluster are now leading global public health problems. Hence, understanding the biological basis of obesity-related pathologies and discovering medical therapies to restore metabolic function is an urgent need for the biomedical community. Therefore, the scientific question of paramount importance is: What is the biology behind the transition from metabolic fitness to illness?

HISTORICAL EVIDENCE FOR METABOLIC AND IMMUNE INTERFACE

A turning point in the study of the biology of T2D was the recognition and statement by H.P. Himsworth in 1936 that there were, in fact, two different types of diabetics: those who were insulin sensitive but simply lacked insulin and therefore presented with disease, and those who did not lack insulin but were insensitive to its effects (7). This delineation of sensitive versus insensitive diabetics paved the way for the study of insulin resistance, but it was not until 1960 and the development of the insulin radioimmunoassay by Berson & Yalow (8) that direct measurement of insulin levels was possible. This advance allowed for the discovery that the insulin-resistant state exhibited hyperinsulinemia. Berson & Yalow themselves went on to demonstrate that the obese diabetic had increased levels of insulin compared with lean controls (9). The ability to measure insulin led to vigorous study of glucose homeostasis in diverse conditions. Importantly, the association between insulin resistance and immune responses was recognized with the identification

of insulin resistance in infectious states, beginning with studies in sepsis (10, 11). It is now appreciated that many diseases with active inflammatory responses display insulin resistance as a feature, such as hepatitis C, HIV, and rheumatoid arthritis (12–14). In addition, early clinical reports that connected the anti-inflammatory drug salicylate with improvements in insulin sensitivity [as summarized elegantly by Shoelson and colleagues (15)] also hinted at potential inflammatory underpinnings to diabetes.

Meanwhile, developing almost in parallel with the concept of insulin resistance was that of insulin antagonists. Scientists used the term "insulin antagonist" to refer to substances that interfered with the action of insulin, and their studies focused on the characterization of known antagonists such as antibodies produced against insulin, growth hormone, and adrenal steroid hormones; insulin-degrading enzymes; and the identification of unknown molecules (16, 17). In one case study, a diabetic patient who acquired gangrene in the foot developed severe insulin resistance. When this patient's serum was used in mice, it provided protection from insulin-induced hypoglycemia, suggesting that the serum contained an insulin antagonist (18). This interesting case again raised the association of infection and its resulting soluble products with insulin resistance and added to it the idea of an insulin antagonist as a mediator of this pathological response. The search at that point did not include inflammatory mediators as possibilities for insulin antagonists but did allow for the existence of unidentified antagonists. As Berson & Yalow (16) stated in an editorial, "The possibility that one or another of the nonantibody antagonists is involved in the causation of diabetes has been suggested on occasion, but remains unproved." Thirty-five years later, a candidate inflammatory mediator from obese adipose tissue, tumor necrosis factor-α (TNF-α), emerged as one such antagonist inhibiting signaling by the insulin receptor (as discussed below).

In the interim period, the evidence continued to mount that T2D patients (those most closely associated with obesity) may be under a unique inflammatory state. Epidemiological studies showed a rise in acute-phase response proteins in serum of T2D patients compared with controls (19, 20). During infections, patients exhibited a state of metabolic demise, including insulin resistance (21–23). However, a specific link between inflammatory and metabolic responses was not yet forged. This connection was later made with the discovery that, compared with lean tissue, obese adipose tissue secretes inflammatory cytokines and that these inflammatory cytokines themselves can inhibit insulin signaling (24–26). These studies first demonstrated the uniting of immune and metabolic pathways and the detrimental effects this relationship can have on cellular and systemic metabolism. The definitive proof of such a connection between inflammatory mediators and insulin resistance in obesity and T2D came from genetic studies that interfered with inflammatory mediators and demonstrated beneficial effects of this interference on insulin action, opening up a new field of study in metabolic diseases (27). We now turn to a more in-depth description of this unique obesity-induced inflammation.

TNF-α: tumor necrosis factor-α

HALLMARKS OF OBESITY-INDUCED INFLAMMATION

Investigators have appreciated for some time now that the inflammatory state induced by metabolic surplus is distinctive and outside the paradigm of classical inflammation as defined by the cardinal signs of redness, swelling, heat, and pain (reviewed in 6, 28). In addition, this classic response is uniformly associated with increased basal metabolic rate and represents the focused and rapid response of the immune system to a site of injury or infection. Normally, such an insult is removed or neutralized, and the inflammation is resolved. However, the inflammatory response found in the obese state is of a different nature (6).

First, the inflammatory trigger in obesity is metabolic and caused by the excess

JNK: c-jun N-terminal kinase

IKK: inhibitor of κ kinase

PKR: protein kinase R

TLR: Toll-like receptor

HFD: high-fat diet

consumption of nutrients (for example, weight loss reverses the inflammation). Not only is the trigger metabolic, but also the specialized metabolic cells (such as adipocytes) are the cells that sustain the insult and whose response begins the inflammatory program, thus mediating the interface between metabolic input and inflammatory output. In other words, metabolic signals emerging from metabolic cells start the inflammatory responses and damage metabolic homeostasis.

The first discovery of inflammation in obese tissues in the mouse revealed increased levels of the cytokine TNF-α in adipose tissue (and in adipocytes themselves) of obese mice compared with lean controls (25). This report was soon followed by a wealth of studies describing the inflammatory differences between obese and lean animals as well as humans. It is now appreciated that not only TNF-α but an array of inflammatory cytokines are increased in obese tissues, including interleukin (IL)-6, IL-1β, CCL2, and others (15, 29). In addition, while predominant, adipose tissue is not the only site of such cytokine expression in obesity; we now know that liver (30), pancreas (31), brain (32), and possibly muscle (33) all experience an increase in inflammatory exposure in the obese state. In certain cases, modest increases have been reported in systemic levels of cytokines or acute-phase reactants in obese animals and humans compared with lean controls (15, 34). Of note, the hallmark of such inflammatory cytokine expression in obese tissues is that it is significant but often modest or local when compared with that of an infection, trauma, or acute immune response.

Investigations upstream of inflammatory cytokine expression identified the kinases c-jun N-terminal kinase (JNK), inhibitor of κ kinase (IKK), and more recently protein kinase R (PKR) as major intracellular contributors to the induction of inflammation in metabolic tissues (35, 36). Compared with lean controls, obese tissues such as adipose and liver display markedly increased activation of these kinases and their downstream signaling cascades. Animal studies utilizing genetic deletion of these kinases also point to their important role in mediating the inflammation found in obesity (30, 36, 37). In addition, the immune sensor known as the inflammasome and the Toll-like receptors (TLRs) of the innate immune system are also activated in obese tissues compared with lean controls (38–40). In sum, multiple signaling pathways in the metabolic cells may be activated upon nutrient excess to stimulate an inflammatory response.

An additional feature of the inflammatory state of obesity is increased infiltration of immune cells into the metabolic tissues. For example, the macrophage population is increased in the adipose tissue of obese mice or mice fed a high-fat diet (HFD) compared with lean mice fed normal chow, and these cells also contribute to the increased tissue cytokine expression (41, 42). Although the factors attracting and/or activating immune cells in obese tissues are not yet fully understood, it has been reported that isolated bone marrow cells migrated toward culture medium conditioned by adipose explants from obese animals (43), displaying the strong connection between obese tissues and immune cell infiltration.

Interestingly, the picture of immune cells has been uncovered to reveal more complexity than simple macrophage infiltration. In adipose tissue, for example, the state of activation of the macrophage population, be it proinflammatory or anti-inflammatory (referred to as M1 or M2 activation, respectively), is important and influenced by metabolic factors. Obese mouse tissues are reported to display an increase in the proinflammatory M1 population of macrophages, which in turn has been shown to negatively affect insulin sensitivity (44). Not only macrophages, but also mast cells and natural killer T (NKT) cells are known to increase in obese adipose tissue compared with lean tissue and may contribute to the inflammatory milieu and metabolic pathophysiology (45, 46). In addition, recent publications reported changes in the adipose tissue T cell populations in obesity (47–49). The ratio of $CD8^+$ to $CD4^+$ T cells increased as animals became obese, and the immunosuppressive T regulatory cells

(Tregs) decreased, creating an environment favorable to immune activation. Although the picture is far from clear, these data show that multiple types of immune cells are involved in the response to the metabolic overload of obesity, particularly in adipose tissue. Future studies will help to elucidate the orchestration of these cell types during obesity, the metabolic signals that engage these effectors, and their contribution to pathological outcomes.

Another hallmark of the metabolic inflammation found in obesity is its chronicity. The occurrences of inflammatory cytokine expression and immune cell infiltration appear to happen gradually and to remain unresolved over time. Again, this is in contrast to the acute inflammatory response normally ascribed to discussions of inflammation where rapid alert, response, and resolution occur at the site of injury. The timing of obesity-induced inflammation in mice needs more careful and exhaustive analysis, although a few studies have begun to investigate the process by observing the inflammatory state of adipose tissue at different time points during the onset of obesity and insulin resistance. Xu and colleagues (41) showed that increases in expression of macrophage-related genes in adipose tissue occurred early after HFD feeding (3 weeks), with a more dramatic increase at 16 and 26 weeks on diet, the latter increase coinciding with the onset of detectable systemic insulin resistance. Their conclusion was that as the fat mass increased, so did the inflammatory gene expression, and the development of insulin resistance intensified this increase. A second study reported a rise in macrophage-specific gene expression from 8 weeks of HFD that increased until the end of the time points studied (weeks 16 and 20) (50). These authors correlated the macrophage infiltration with an increase in adipocyte cell death and hypothesized that the macrophages may be responsible for the removal of the dead cells and remodeling of the adipose tissue. The issue of resolution or tissue remodeling in obesity is an intriguing but underexplored area. It would seem that the inflammatory state induced by metabolic overload may not be dramatic enough to stimulate a full resolution program, and therefore the low-grade signals coming from the metabolic tissues are maintained in a chronic state. Or it could be that a type of resolution unique to metabolic inflammation occurs that includes the turnover of adipocytes or other unknown events. Finally, the metabolic origin of this inflammation may preclude the mounting of a resolution response. This deficiency of resolution may be due to an obesity-induced defect or lack of evolutionary selection to develop such a response to metabolic signals.

There is also evidence that inflammatory responses may be acutely evoked by nutrients. For example, administration of lipids into mice for a few hours results in inflammatory responses such as activation of JNK in skeletal muscle and liver tissues (51). Studies in humans also indicate that nutrients may invoke a more rapid inflammatory response. Work by Aljada and colleagues (52) showed that within hours after ingestion of a high-fat, high-carbohydrate meal, the circulating blood polymorphonuclear and mononuclear leukocytes exhibited signs of reactive oxygen species (ROS) and NF-κB activation. The issue of the timing and progression of the obese inflammatory response still requires careful time course studies, but one hypothesis is that the inflammatory signals occur at both early and later stages. For example, small signals that occur in response to nutrient overload (or even certain inflammatory nutrients) may build up over time to result in more major changes such as immune cell activation and infiltration. This question of the timing of metabolic-induced inflammation is intriguing, as it now points to the possibility of identifying specific nutrient-induced immune responses. This is addressed further below.

Importantly, the inflammation discovered in obese tissues in the mouse has also been reported in humans. First, several studies describe inflammatory cytokine induction, increased kinase activity, and even macrophage infiltration in the adipose tissue of obese humans when compared with their lean cohorts (25, 53–55). Second, serum levels of inflammatory

IRS-1: insulin receptor substrate 1

mediators such as C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1), and even white blood cell count in humans are associated with an increased risk for development of T2D (56–58). Third, recent large-scale genetic analyses have revealed significant systemic links between obesity and metabolic syndrome phenotypes and inflammatory gene networks (59, 60).

In summary, the hallmarks of obesity-induced inflammation are that it (*a*) is metabolic—a nutrient-induced inflammatory response orchestrated by metabolic cells; (*b*) is moderate—low-grade and local expression of inflammatory mediators induced by stress sensors such as IKK and JNK; (*c*) creates a modified milieu—altered composition of immune cells favoring a proinflammatory tissue environment; and (*d*) is maintained—chronic maintenance of the inflammatory state without apparent resolution (**Figure 1**). Finally, unlike the classic paradigm, this inflammatory state is associated with a reduced metabolic rate. Therefore, given the features discussed above, we may venture to name this unique state of inflammation in order to distinguish it from the classical definition. We propose "metaflammation" to clarify the inflammatory state in question in obesity.

WHAT IS THE EFFECT OF METAFLAMMATION IN OBESITY?

After describing the inflammation that occurs during the nutrient and energy overload of obesity, the natural next question to ask is what its effects are on tissue and organismal metabolism. There is strong evidence to conclude that activation of the inflammatory pathways interferes with normal metabolism and disrupts proper insulin signaling. We describe these alterations in each of the major metabolic tissues specifically.

Adipose Tissue

We begin in the adipose tissue, the site where inflammatory alterations were first described and are most studied in obesity. Inflammatory mediators in adipose tissue can cause insulin resistance in adipocytes. For example, TNF-α-treated adipocytes display decreased insulin signaling and subsequently decreased glucose uptake (61–63). This discovery led to or paralleled work in cells identifying the major intracellular pathways responsible for the blockade of insulin signaling. The identified pathways involve the inflammatory kinases discussed above. In response to nutrient or inflammatory signals, JNK and/or IKK are activated and can target insulin receptor substrate 1 (IRS-1) for serine phosphorylation, which inhibits the insulin receptor signaling cascade. An interesting area of future research is the identification of other cellular substrates targeted by these kinases as it relates to metabolic regulation. Not only JNK and IKK, but also other kinases such as PKR, S6K, protein kinase Cθ (PKCθ), extracellular signal–regulated protein kinase (ERK), and mammalian target of rapamycin (mTOR) can also target IRS-1 for inhibitory phosphorylation (64), implying that activation of diverse cellular networks can antagonize insulin signaling. The consequence of such diversity is that when a tissue is exposed to excess nutrients, multiple signaling networks are activated and may contribute to inflammatory signaling. Therefore, one single kinase, one signal target, or a linear pathway will not be the sole response to the nutrient or the only conductor of the inflammatory response, and a perspective of a network would be instrumental in our explanations of nutrient-induced insulin resistance or other metabolic adversities.

The inflammatory kinases not only inhibit insulin action through targeting insulin signaling molecules, but they also regulate downstream transcriptional programs through the transcription factors activator protein-1 (AP-1), NF-κB, and interferon regulatory factor (IRF), resulting in increased expression of proinflammatory cytokines (**Figure 2**). These cytokines then feed into the inflammatory response and exacerbate the inhibitory signaling of metabolic pathways. As a stress kinase, PKR can also affect general translation within the cell by inhibiting the translation initiation

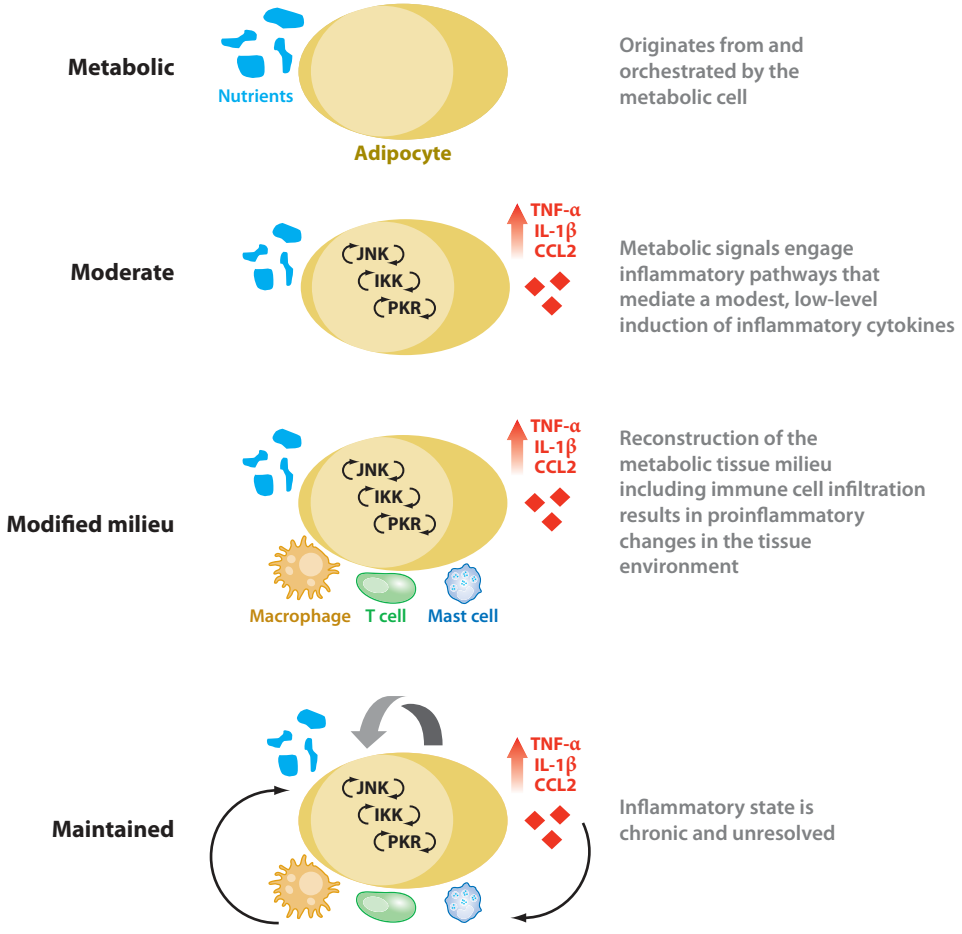

Figure 1

Hallmarks of metaflammation. The first feature of obese inflammation is that the initiation is metabolic—it originates from metabolic signals and within metabolic cells such as the adipocyte. Second, the metabolic signals trigger inflammatory intracellular signaling pathways that mediate the downstream inflammatory response such as the JNK, IKK, or PKR pathways. The activation of these mediators induces inflammation in metabolic tissues that is moderate—a low-level induction of cytokines such as TNF-α, CCL2, or IL-1β occurs in response to the excess nutrients. Over time, this low-grade inflammation may induce the recruitment and activation of many professional immune cells, driving the metabolic tissue toward a modified milieu—increases in macrophages, mast cells, and various T cell populations result in a stronger proinflammatory response and drive inhibition of metabolic cell function. The inflammation induced by nutrient excess is maintained—no apparent resolution of inflammation is observed, and the inflammatory pathways continue to reinforce each other, from metabolic cell signals of distress to immune cell responses. Finally, unlike the classic inflammatory paradigm, metaflammation is associated with reduced metabolic rate. (Abbreviations: IKK, inhibitor of κ kinase; JNK, c-jun N-terminal kinase; PKR, protein kinase R; TNF-α, tumor necrosis factor-α.)

factor eIF2α (eukaryotic translation initiation factor 2α), further complicating the action of anabolic pathways. Other mechanisms that contribute to the inflammatory origin of insulin resistance are under investigation and may involve SOCS (suppressor of cytokine signaling) proteins involved in the degradation of IRS-1 (65), as well as organelle dysfunction (66).

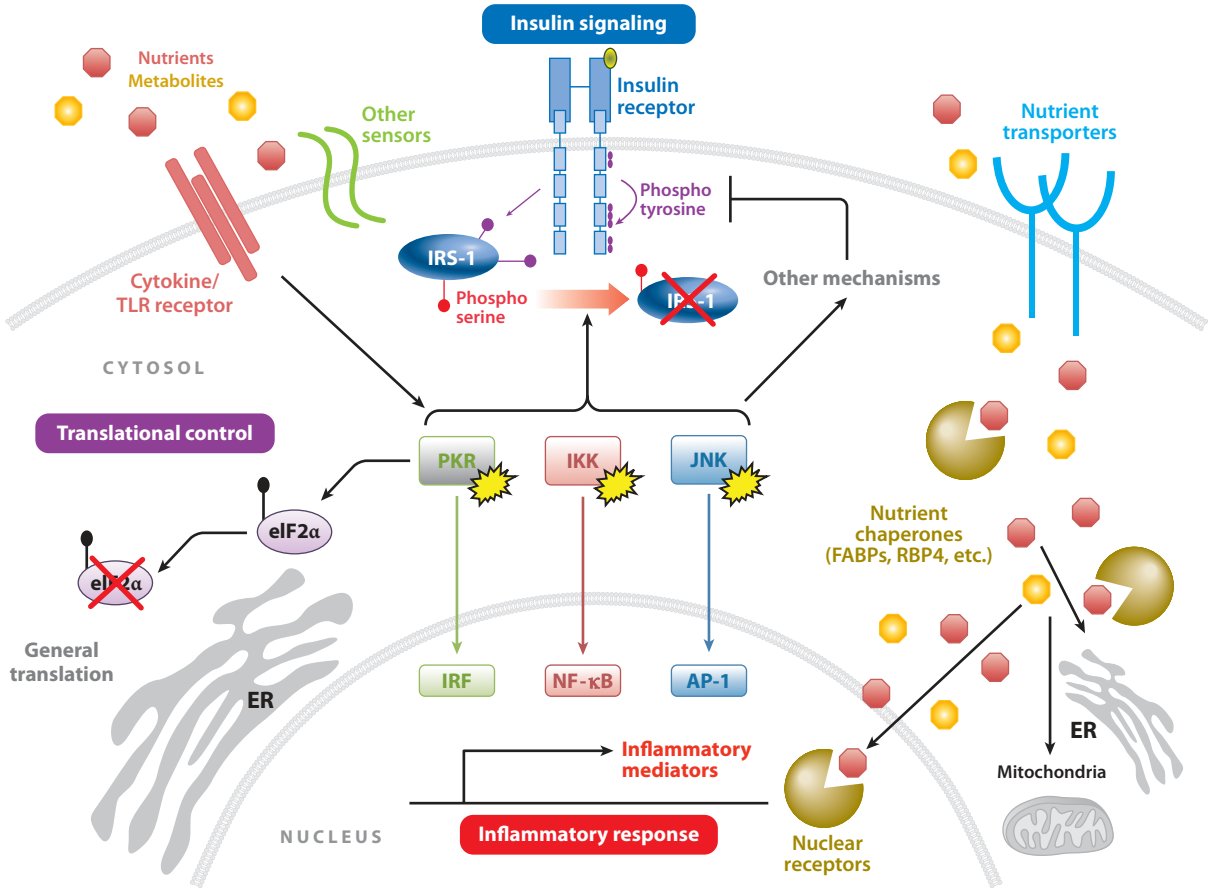

Figure 2

Inflammatory disruption of metabolic functions. Obese or high-fat diet conditions lead to the induction of inflammatory signaling pathways in metabolic cells through several paths. Nutrients or other metabolites may result in the activation of cytokine or Toll-like receptor (TLR) pathways and have access to cellular targets directly or via chaperoning molecules. Three prominent kinases downstream of these receptors are JNK, IKK, and PKR, which play important roles in relaying stress signals throughout the cell and engaging metabolic responses. All three of these kinases can inhibit insulin signaling via serine phosphorylation of IRS-1. This phosphorylation leads to the ubiquitination and degradation of IRS-1, thus blocking insulin action downstream of receptor activation. In addition, PKR can negatively regulate the translation initiation factor eIF2α, leading to inhibition of general translation, and influence ER function. This property of PKR suggests that inflammatory signaling cascades, ER function, and insulin action may be regulated through metaflammation complexes or metaflammasomes containing these kinases. These three kinases can induce an inflammatory response through activation of the transcription factors AP-1, NF-κB, and IRF, which upregulate inflammatory mediator gene expression. The increase in inflammatory cytokines can then lead to exacerbated receptor activation as the cytokine signals combine with excess nutrients and establish a positive feedback loop of inflammation. (Abbreviations: AP-1, activator protein-1; eIF2α, eukaryotic translation initiation factor 2α; ER, endoplasmic reticulum; FABP, fatty acid–binding protein; IKK, inhibitor of κ kinase; IRF, interferon regulatory factor; IRS-1, insulin receptor substrate 1; JNK, c-jun N-terminal kinase; PKR, protein kinase R; RBP, retinol-binding protein.)

The functional link between inflammatory signaling and insulin resistance has also been demonstrated in vivo. Indeed, genetic loss-of-function mouse models for TNF-α, TNFR1/2, JNK, TLR2, IKKε, and others have all demonstrated beneficial metabolic effects from lack of their respective inflammatory mediators when the animals are challenged with obesity or

HFDs (27, 37, 67–69). For example, TNF-$\alpha^{-/-}$ mice undergoing diet-induced obesity display decreased blood glucose and insulin levels compared with control mice, along with improved glucose and insulin sensitivity (27). Importantly, these models have also shown a preservation of local insulin signaling and sensitivity in adipose tissue when the inflammatory mediators are absent, indicating that protection of insulin signaling in the specialized metabolic tissues leads to systemic improvements.

The effects of inflammation in adipose tissue are not limited to insulin signaling alone. For instance, treatment of adipocytes in vitro with inflammatory cytokines such as TNF-α can induce lipolysis, itself a feature of obese adipose tissue pathology (70). In addition, inflammatory signaling in the adipocyte can also downregulate the activity of the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ), which is essential to adipogenesis and to maintenance of adipocyte gene expression and function (71). In support of this finding, TNF-α treatment blocks the differentiation of preadipocytes in vitro (72). Indeed, without PPARγ the adipocyte's ability to make and store lipids and to maintain insulin sensitivity is compromised (71). One important consequence of inflammation-induced PPARγ downregulation is reduced adiponectin expression, a cytokine specific to adipocytes that is also involved in regulating systemic insulin sensitivity (73). Relief of inflammation restores the adipocyte's capacity for lipogenesis and adiponectin expression (74). Therefore, collectively we observe that the effects of inflammation on adipose tissue are multifaceted but seem to have one goal in common: shutting down normal adipocyte processes in favor of stress responses. Without the proper functioning and endocrine action of adipose tissue, the body's nutrient deposition is disrupted, and systemic glucose homeostasis is thrown into imbalance.

Immune Cell Contribution

The work described above focuses on isolated adipocytes or germ-line genetic models involving inflammatory mediators where deletion occurs in every tissue. Given that immune cell infiltration is one of the hallmarks of obese inflammation, many researchers have focused on immune cell studies, primarily of macrophages, to determine the effects of the immune cells on adipose tissue function. Deletion of macrophage-specific genes of various inflammatory signaling components has revealed the contribution of macrophage functions in obesity-induced insulin resistance. For example, deletion of the chemoattractant receptor CCR2 in HFD-fed mice resulted in decreased macrophage infiltration into adipose tissue, a decrease in adipose inflammatory gene expression, and also improved insulin sensitivity compared with control animals (75). Conversely, overexpression of the chemoattractant CCL2 specifically in adipose tissue causes increased macrophage infiltration and results in systemic insulin resistance and hepatosteatosis (76, 77). Again, in these studies the animals were carrying germ-line deletions; therefore, macrophage-specific effects were not distinguishable. To answer the question about macrophage-specific effects, several studies have utilized macrophage-specific deletion or bone marrow transplant models to pinpoint macrophage/myeloid contribution in the obese inflammatory phenotype. Deletion of IKKβ in the myeloid lineage protected mice on HFDs from glucose intolerance (78). Additional studies investigating Cbl-associated protein (Cap), CCR2, fatty acid–binding protein 4 (FABP4/ap2), and TLR4 loss of function in macrophages also revealed decreases in obesity-induced inflammation and insulin resistance of varying degrees (43, 79–81). Interestingly, myeloid-specific deletion of JNK was not associated with a beneficial metabolic phenotype, supporting the conclusion that activity of inflammatory pathways in cells such as adipocytes is sufficient for obesity-induced insulin resistance and metabolic deterioration (82, 83). The only studies reporting advantageous molecules in the macrophages were done with PPARγ and PPARδ. Loss of PPARγ or PPARδ in macrophages actually worsens

the metabolic phenotype of the mouse, and this has been attributed to a failure of the M2 alternate activation of the macrophages and a subsequent switch to a proinflammatory state (84, 85). Therefore, a general conclusion drawn from these studies is that interference with the proinflammatory action of the macrophage is beneficial for the adipose tissue environment and organismal glucose homeostasis.

What about removing entire cell types? Taking these investigations one step further, many groups have used techniques that deplete entire cell types in the immune population. For instance, one study depleted mice of $CD11c^+$ immune cells, which include macrophages, dendritic cells, and neutrophils, among other immune cells, and showed that insulin sensitivity was improved in these obese animals (86). Studies involving T cell populations also demonstrated that depletion of $CD8^+$ T cells or transfer/enhancement of $CD4^+$ T cells or Tregs improved the insulin sensitivity of diet-induced obese mice (47–49). Finally, studies in mast cells and NKT cells also showed that depletion of these cell types leads to decreased inflammation in the adipose tissue and improvements in glucose homeostasis (45, 46). Again, the data seem to point to the inflammatory actions of the immune system as important contributors to the disruption of metabolic function, and when these are removed it is beneficial for the anabolic insulin pathways. This benefit can occur whether you are manipulating the system to act in an anti-inflammatory manner (for example, adoptive transfer of Tregs) or inhibiting its proinflammatory actions (i.e., through gene deletion of chemoattractants). In sum, in the adipose tissue we see the outcropping of inflammation leading to inhibition of insulin signaling and other adipocyte anabolic functions through complex interactions between adipocytes and a series of immune effectors. Taken together, large amounts of data point to a causal role of adipose inflammation in the manifestation of obesity-induced insulin resistance.

Liver

The liver represents another major metabolic organ in its ability to control not only gluconeogenesis and glycogen storage, but also massive amounts of lipogenesis and cholesterol synthesis and secretion. In contrast to adipose tissue, the liver does not experience an infiltration of macrophages during the onset of obesity but instead undergoes an activation of inflammation within cells of the liver, including the resident macrophage-like Kupffer cells (87). In animal models of obesity, inflammatory cytokine expression is increased in the liver compared with lean controls (30). Indeed, obesity is associated with fatty liver (or hepatosteatosis) that often leads to the more advanced inflammatory state of steatohepatitis. What effects does this inflammation have on liver metabolic functions?

First, as described in adipose tissue, inflammatory mediators have the ability to inhibit insulin signaling, and these same inhibitory pathways have been shown to be active in the obese liver (88). Specifically, activation of the NF-κB pathway appears to be critical in inflammation-induced insulin resistance. Mice with liver-specific activation of IKKβ display decreased glucose tolerance and insulin sensitivity and decreased insulin signaling in the liver itself (30). Conversely, a loss of IKKβ in hepatocytes decreased the HFD induction of inflammatory cytokines in the liver and rendered the mice more insulin sensitive (78). This reduction in insulin sensitivity and signaling affects other aspects of liver metabolism, most notably gluconeogenesis. Normally, gluconeogenesis is suppressed by insulin signaling, but in obese conditions this regulation is lost, and hepatic glucose production subsequently contributes to hyperglycemia. Again, upon inhibition of inflammatory signaling, gluconeogenesis is properly suppressed by insulin (78). JNK kinase is also activated in the liver during obesity, and loss-of-function models have revealed decreased inflammatory markers and increased insulin sensitivity in the liver of HFD-fed $JNK1^{-/-}$ mice (37). Interestingly, unlike whole liver inhibition of JNK, hepatocyte-specific

deletion of the JNK1 isoform resulted in glucose intolerance and increased glucose and lipid production in the liver of lean mice (89). In this setting, neither the impact of the remaining JNK isoforms (JNK2 or 3) nor the effects of obesity have been addressed. A possible explanation for the discrepancy of liver JNK action is that JNK activation may operate on multiple cell types in the liver (such as hepatocytes, Kupffer cells, and others) and that this collective action is detrimental for metabolism. This hypothesis is supported by the inhibitor studies using small molecules, dominant-negative JNK, and RNAi-mediated blockade of JNK activity, all of which affected multiple cell types in the liver and resulted in increased insulin sensitivity and improved systemic metabolism (90–93).

Lipogenic effects of inflammation are an important but understudied area. Early studies have shown that in vivo administration of TNF-α or IL-6 can induce hepatic lipogenesis and increase hepatic triglyceride production (94, 95). This augmented production leads to an increase in very-low-density lipoprotein (VLDL) (and particularly apoB100) secretion from the liver and an overall increase in serum triglyceride levels. Although it seems that inflammatory cytokines can induce lipogenesis pathways in the liver, mechanistically this process is not well understood and necessitates further study. Another effect of inflammation in the obese liver is the activation of a secretory response involving inflammatory mediators and acute-phase reactants. For example, serum levels of cytokines such as CRP, PAI-1, serum amyloid A, and IL-6 produced by the liver are increased in obese animals and humans compared with lean controls (15, 34). Some of these cytokines have been shown to have adverse metabolic effects on peripheral organs. One study found that liver IKK activation leads to an increase in systemic IL-6 that negatively influences muscle insulin sensitivity (30). Therefore, the secretory profile of the liver in obesity may be a strong contributor to the malfunction of peripheral tissues under such nutrient excess.

If the inflammation in the liver escalates, cell death may occur, resulting in the recruitment of immune cells and the pathological state known as steatohepatitis. The stress kinase JNK has been shown to be required for saturated free fatty acid–induced apoptosis in hepatocytes, providing a possible link between the excess lipids of obesity and the resulting inflammation-induced cell death (96). Thus, the liver remains an important site where metabolic and immune cell signals converge to limit the tissue's response to nutrients.

Muscle

The muscle is a key site of glucose uptake and energy consumption in the body and in this capacity is an important contributor to glucose homeostasis. Consensus has not been reached regarding the data on muscle inflammation in obesity, and many of the following points may be debated. Thus far, obesity does not appear necessarily or uniformly to induce inflammation in muscle tissue, but inflammatory mediators from other sites such as liver and adipose can influence muscle metabolism (30, 97). For example, morphologically, macrophage infiltration is not observed in muscle fibers per se in obese animals, but the adjacent adipose tissue displays increased infiltration compared with lean tissues (42). Also, unlike adipose or liver tissues, muscle does not express or release significant amounts TNF-α or IL-6 in T2D patients compared with controls and therefore is not likely to be a source for the rise in inflammatory mediators (98, 99). However, data contrary to this also exist, as local increases in TNF-α expression in muscle tissue of obese humans reportedly correlate strongly with impaired insulin sensitivity (33). Mechanistic studies in mice activating the IKK/NF-κB pathway in muscle reveal a muscle wasting phenotype but no induction of inflammatory cytokines (100). Inhibition of the NF-κB pathway through muscle-specific repression of NF-κB or deletion of IKK2 also revealed no effect on muscle insulin sensitivity or systemic glucose homeostasis, leading to the conclusion that at least this major inflammatory pathway does not appear to regulate muscle metabolic

dysfunction during obesity (100, 101). Muscle-specific deletion of JNK1 also presents with complex results, displaying increased insulin sensitivity in the muscle but impaired liver and adipose tissue metabolism and, as a result, no systemic benefit (102).

Although the muscle cell does not seem to be an origin of inflammatory signals in obesity or to regulate metabolism through inflammatory kinase action, the influence of peripheral inflammation on muscle function is well established. For example, inflammatory cytokines are able to induce insulin resistance in muscle cells in culture (103, 104) and in vivo by infusion into humans, resulting in decreased glucose uptake and glycogen synthesis (105). It has been proposed that TNF-α, IL-6, CCL2, and/or retinol-binding protein-4 are inflammatory mediators from sources such as adipose and liver tissue that can act on the muscle (30, 97, 103). Indeed, the $TNFR^{-/-}$ mouse is resistant to the decrease in muscle glucose uptake and insulin resistance in response to TNF-α administration (106), and treatment with antibodies to TNF-α can increase muscle insulin sensitivity (107). In addition, liver-specific activation of IKK in mice results in increases in systemic IL-6 levels. The muscle displays increased IL-6 signaling and decreased insulin sensitivity and glucose uptake. When antibodies to IL-6 are administered, muscle IL-6 signaling is decreased and glucose homeostasis improves (30). The role of IL-6 in muscle insulin sensitivity is controversial and complex, however. Several studies report no effect or insulin-sensitizing effects of IL-6, as in the context of exercise-induced IL-6 release from muscle (reviewed in 108).

Given that muscle is a tissue of paramount importance for glucose uptake and glycogen synthesis, further studies are necessary to elucidate the connections between muscle metabolism and inflammatory pathways during obesity.

Brain

Although not usually classified as a metabolic organ per se, the brain is the site of central regulation of appetite control and energy expenditure. The brain, and specifically the hypothalamus, responds to metabolic endocrine signals, including nutrients themselves, insulin released from the pancreas, and leptin secreted from the adipose tissue. Insulin and leptin both have important appetite-suppressant effects mediated through hypothalamic signaling. Interestingly, in obesity the hypothalamus itself exhibits both insulin and leptin resistance, leading to a loss of this control of appetite and feeding behavior, exacerbating the already excessive body weight gain (reviewed in 109). In addition to influencing appetite, the central nervous system can also influence peripheral organ response to nutrients, as seen in hypothalamic control of hepatic glucose production (110). Intriguingly, more recent studies have revealed that inflammatory pathways in the hypothalamus are also activated during obesity. De Souza et al. (32) reported an increase in expression of TNF-α, IL-1β, and IL-6, among other immune-related molecules, in HFD-fed rats compared with lean controls. In addition, HFD-fed rats display evidence of increased apoptosis in the hypothalamus (111). What are the effects of such inflammation in the brain and subsequently on metabolic homeostasis? Again, the few studies available on this subject point to a relationship not only with insulin resistance but also with leptin resistance and the resulting feeding behavior and energy expenditure. For example, in HFD-fed mice, brain-specific activation of the inflammatory kinase IKKβ resulted in an increase in food intake and body weight along with significant hypothalamic insulin and leptin resistance (112). Conversely, inhibition of IKKβ signaling in the brain restored insulin and leptin sensitivity and protected mice from HFD-induced weight gain, resulting in overall improved glucose homeostasis. Further evidence to support the idea that brain inflammation may play a causal role in obesity-induced insulin resistance comes from studies done upstream of IKK signaling, namely in the TLR pathway. The TLR pathway of the innate immune system is involved in sensing

pathogens and eliciting a proper immune response. It is thought that under HFD conditions, saturated fatty acids themselves may activate TLR signaling. Infusion of a TLR4 antibody via intracerebroventricular canulation protected rats from the inflammatory response elicited by saturated fatty acids and concomitantly decreased food intake and body weight gain (113). In addition, brain-specific deletion of MyD88, a downstream adaptor molecule for TLR signaling, enhanced leptin signaling in HFD-fed mice compared with control littermates (114). This recovery of leptin signaling was accompanied by a decrease in food intake and weight gain and improvements in glucose homeostasis. The role of the JNK kinase in central regulation of metabolism is substantial, yet complex. Studies utilizing brain-specific deletion of JNK1 under HFD conditions demonstrated protection against insulin resistance, hyperinsulinemia, and glucose intolerance in the mice lacking JNK1 compared with controls (115, 116), implicating the brain as a key site of JNK action. However, mice that have undergone JNK1 brain deletion are smaller than their wild-type counterparts and exhibit increased thyroid hormone signaling and thermogenesis. Therefore, further study is needed to distinguish the effects on general body growth from those on energy metabolism and adiposity. Nonetheless, the advances described above reveal that inflammatory pathways in the brain during obesity may be major players in the imbalance of systemic metabolic homeostasis by contributing to inhibition of insulin and leptin signaling and thereby impeding regulation of food intake, body mass, and systemic metabolism.

Pancreas

The pancreas is at the heart of glucose homeostasis, given its role as the source of insulin and glucagon production. Failure of this organ to produce sufficient insulin in response to rising systemic glucose levels is at the center of diabetic disease. Although the immune origin of type 1 diabetes has long been appreciated, given the autoimmune mechanism that destroys the insulin-producing β cells, evidence is now accumulating to implicate inflammation in the dysfunction of the T2D pancreas. During the course of obesity, peripheral insulin resistance requires ever increasing amounts of insulin to remove glucose from the circulation. This increased production results in stress on the β cell, eventually leading to its hyperproliferation and surrender to apoptosis.

Indeed, recent data have shown that during the time course of a HFD, inflammatory cytokine expression in the pancreas increases and macrophage infiltration occurs, in parallel with the onset of glucose intolerance (31). Inflammatory activity in the pancreas has long been known to disturb insulin production and β cell survival, two of the main mediators being IL-1β and IFN-γ. IL-1β activates the NF-κB pathway in pancreatic islets, and the effects of this activation have been studied in the pancreas using a nondegradable inhibitor of NF-κB signaling known as IκBα. Overexpression of this inhibitor in human islets in vitro protects cells from IL-1β-induced nitric oxide (NO) production and apoptosis (117). A transgenic mouse expressing this same inhibitor specifically in β cells also resulted in decreased NO production and apoptosis in response to inflammatory cytokines and significant in vivo protection from streptozotocin (STZ)-induced diabetes, a disease model characterized by selective β cell loss (118). JNK signaling has also been implicated in pancreatic protection from apoptosis: JNK1$^{-/-}$ mice are resistant to STZ-induced diabetes (119), and expression of a dominant-negative JNK in transplanted islets elevated insulin levels and decreased blood glucose in STZ-treated mice (120). In cultured cells, JNK inhibition protects from loss of insulin gene expression and secretion induced by oxidative or cytokine stress (120, 121). Thus, these two kinases at the core of inflammatory signaling can affect major β cell functions such as insulin production and survival.

However, what is really needed to understand these processes are studies in the context of obesity. The work described above

investigates inflammatory molecules in isolated β cells or in pancreas-destroying models of diabetes. Obesity differs from these models in its distinct features of lipid overload, peripheral insulin resistance, and slowly progressing time course of pathology. Studies in pancreas-specific genetic models performed during the development of obesity and T2D will be useful to investigate the role of inflammatory mediators on pancreatic β cell function. For example, it has been hypothesized that low-level inflammation in the pancreas (namely IL-1β expression) may promote β cell proliferation and that only exacerbated inflammation results in apoptosis (122). Given that one of the characteristics of obesity-induced inflammation is a low level of cytokine expression, this may drive islet hyperproliferation and be needed for adaptation to peripheral insulin resistance. However, this adaptive hyperinsulinemia itself can also be a driver of metabolic complications. As a result, it is favorable to inhibit inflammation as conditions worsen to preserve β cell survival and function for the organism.

Inflammatory Mechanisms in the Gastrointestinal Tract

One exciting new area of discovery is the influence of gut microbiota upon obesity and metabolism. The interactions between microbes of the intestine and host responses can affect weight gain, insulin sensitivity, and the inflammatory state, not only of the gut but of peripheral organs as well.

A first critical observation in this area came with the discovery that populations of gut microbiota are significantly different between lean and obese animals (123). Specifically, at the division level genetically obese (ob/ob) mice display decreased levels of Bacteroidetes with an increase in Firmicutes bacteria compared with lean controls. A similar population change was also shown to be present in obese versus lean humans (124), and changing the diet to promote weight loss was able to change the microbiota profile toward a lean phenotype. Intriguingly, this altered flora has a potential activity of its own, as transfer of obese gut microbiota to lean mice caused them to gain more weight when compared with mice receiving wild-type microbiota (125). The mechanism behind this difference is thought to be increased energy harvest in the obese intestine due to its specific microbiota makeup, although further study is needed to fully understand the process behind this phenomenon.

The picture becomes more complex when the inflammatory status of the intestine is considered. The idea that inflammation of the gut could play a role in determining body weight was supported by the fact that transfer of microbiota from normal or conventionalized mice into germ-free mouse donors caused a significant weight gain accompanied by increased insulin resistance (126). In addition, germ-free mice were protected from body weight gain, insulin resistance, and glucose intolerance induced by HFD compared with conventionalized mice (127). More specifically, studies investigating the bacterial cell wall component lipopolysaccharide (LPS), which activates the host's innate immune system through TLR4, reveal a relationship between HFD and increased levels of LPS exposure (128). In addition, a study in rats reported that those animals with a propensity for obesity displayed altered gut microbiota and increased TLR4 activation (129). Treatment of obese mice with antibiotics decreased levels of LPS and TNF-α expression in the intestine and led to a decrease in body weight and serum insulin and improvements in glucose tolerance (130, 131). Finally, one intriguing study provides evidence that host inflammatory mediators can actually influence intestinal microbiota and whole body metabolism. Vijay-Kumar et al. (132) report that $Tlr5^{-/-}$ mice develop obesity along with features of metabolic syndrome including glucose intolerance, fatty liver, insulin resistance, and islet hyperplasia. Of note, transfer of gut microbiota from $Tlr5^{-/-}$ cecum to wild-type recipients recapitulated some aspects of the metabolic syndrome phenotype in the wild-type animals. The

metabolic phenotype in these animals is mild, however, and not likely to account for the extent of pathology observed in the obese, type 2 diabetic state. The transferred Tlr5$^{-/-}$ microbiota also resulted in increased TNF-α and IL-1β in the colon of recipient animals, pointing to enhanced inflammation as a possible factor in the regulation of the metabolic phenotype. In sum, these observations support the concept that bacterial and host interactions within the gastrointestinal tract may influence systemic metabolic homeostasis and point to inflammatory molecules as potential mediators of these effects. This is an important area to explore, as our understanding of the communication of the various microbes to the complex array of host tissues and cell types is limited; research into this area will uncover these interactions and their influence on whole body metabolism.

HOW DOES METABOLIC INFLAMMATION OCCUR?

We now come to the question of how the inflammatory response occurs in obesity in the first place. Starting signals for a traditional inflammatory response are usually described in terms of pathogens—a molecule from a microbe, parasite, foreign body, or injured tissue—that will engage a cell signaling pathway (either in the host cell or sentinel immune cell) to initiate an immune response. With overfeeding or HFDs, however, the starting signal is unclear and remains a critical area of future research. Although the initiating factor is not fully known, it is thought that the insult-to-signaling pathway originates within the specialized metabolic cell, e.g., in the adipocyte, hepatocyte, or myocyte. As even nonimmune cells possess their own defensive mechanisms, these metabolic cells are fully capable of engaging inflammatory signaling and communicating in response to danger signals. For example, the adipocyte can execute many of the downstream inflammatory signaling events such as inflammasome and TLR activation, JNK and NF-κB signaling, and production of inflammatory cytokines in response to metabolic stress signals that are normally viewed as the territory of professional immune cells.

One theory to explain the origin of the inflammatory response in obesity is that nutrients themselves are naturally inflammatory. That is to say, there is a normal physiological response from metabolic cells encountering nutrients that results in a low level of inflammation. The idea is that food or nutrients are not self and therefore elicit a slight immune response as they are encountered and metabolized. Indeed, digestion of food and its metabolic trafficking is a daily yet intense experience as cells encounter the flood of energy and nutrients in a short period of time (i.e., lunch), and such a stimulus may be anticipated to induce a brief episode of stress signaling in the target cells. If this is the case, then there may be mechanisms to mitigate this physiological nutrient response in metabolic cells and tissues. One study supporting this hypothesis demonstrated that the six-transmembrane protein STAMP2 may play just such a role in metabolic tissues encountering nutrients (133). STAMP2 expression was increased in adipose tissue during feeding and displayed anti-inflammatory properties in response to nutrient stimulation in adipocytes. When cultured adipocytes lack STAMP2, they produce an uncontrolled inflammatory output when exposed to nutrients. Indeed, Stamp2$^{-/-}$ mice exhibited increased adipose tissue inflammation when fed a regular diet and systemic metabolic dysfunction such as insulin resistance and glucose intolerance. These results suggest that STAMP2 may function as an immune suppressor in metabolic and immune cells as they respond to nutrients. Under obese conditions, the upregulation of STAMP2 expression during feeding is lost, correlating with increased inflammatory conditions. While the STAMP2 molecule possesses a metalloreductase/oxidoreductase activity, the exact substrates to which it responds or the molecular mechanisms by which it prepares the cells for incoming nutrients and prevents inflammatory responses remain important areas of future research.

A second hypothesis is that feeding naturally couples the nutrients with inflammatory molecules. For example, there is increased permeability of the intestine after feeding, probably to ensure maximal nutrient uptake. Interestingly, studies in mice and humans revealed that serum LPS was increased after feeding, suggesting the hypothesis that intestinal permeability releases inflammatory molecules into the circulation, coupling nutrient entry with inflammatory signals (128, 134). Therefore, the metabolic cells would adapt to coping with both. In lean animals postfeeding or during fasting, levels of nutrients and LPS are low, indicating the system has effectively handled the nutrient load. However, in obese animals the intestine is constantly more permeable than in lean animals, and serum levels of LPS are higher, indicating that the system no longer functions efficiently and there may be a constant source of inflammatory signal present. Higher LPS levels in obesity could also be explained in that increased nutrient/LPS exposures heighten the baseline inflammatory response of metabolic tissues.

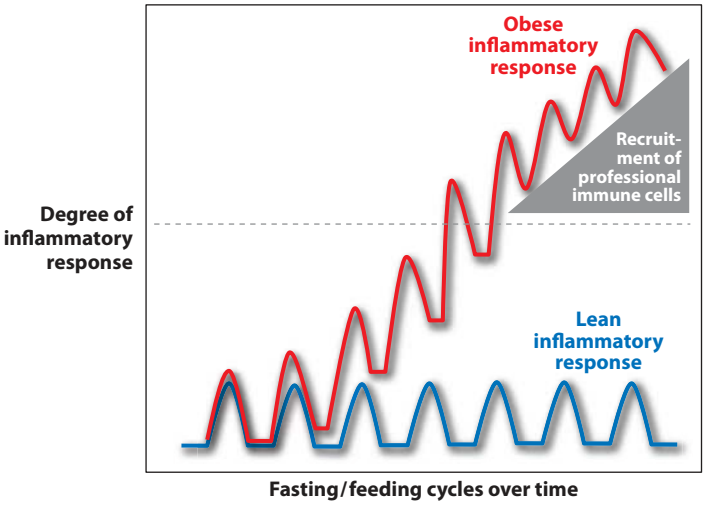

Figure 3

Pulsatile inflammatory response during feeding: normal versus obese reactions over time. Fasting/feeding cycles induce low-level inflammatory responses in metabolic cells of lean, healthy animals that are easily resolved. During the high-fat diet or excess feeding of obesity, responses to food become more intense and frequent, and resolution of the inflammatory response becomes less efficient, raising the baseline of inflammation in metabolic tissues. Once the level of inflammatory response reaches a certain threshold in the metabolic cells, professional immune cells such as macrophages, mast cells, and T cells are recruited and activated. Their participation in the inflammatory response alters the tissue environment toward a proinflammatory milieu and exacerbates the inflammation even further.

Hence, a general hypothesis may be drawn from the two examples given above, as follows: During the feeding/fasting cycle, a pulsatile inflammatory response occurs in the metabolic cells (**Figure 3**). Under normal conditions, the low-level inflammation peaks with feeding and resolves after the nutrients are metabolized. With overfeeding or obese conditions, however, a constant stimulus from nutrient intake results in a more consistently active inflammatory response. These low-level signals accumulate over time, amplify with each nutrient exposure, begin to impair normal metabolic pathways, and may reach a level where the professional immune cells are alerted and called to duty. Once the immune cells are activated and participate in the response to inflammation, the severity of the response increases, and disruption of metabolic cell function becomes more complete.

Another theory to explain the origin of the inflammation found in obesity is that the nutrients themselves are not naturally inflammatory but in excess can engage the classical pathogen-sensing or immune-response pathways. This is almost a mistaken identity theory—the system is tricked into thinking that these abundant nutrients are pathological. This mistaken identity may be due to a dose-dependent loss of specificity that exploits the ability of pathogen sensors to recognize similar structural entities, such as lipids. We focus on two examples from the literature that may support this hypothesis. The first is in the study of TLRs, the pathogen-sensing receptors of the innate immune system. Again, as the specialized metabolic cells possess their own defense system, they express various TLRs. Adipocytes, for example, express functional TLR4 and TLR2. Studies in mice have revealed that adipose TLR4 can be activated by infusion of saturated fatty acids and that this activation contributes to the resulting insulin resistance (39). Also,

increasing the level of fatty acids in the system via HFD feeding causes an increase in TLR4 expression, and genetic loss of TLR4 in these conditions may ameliorate insulin resistance (81, 135).

A second example is the pathogen-sensing kinase PKR, known to sense double-stranded RNA, which is indicative of viral invasion of the cell, and to initiate an inflammatory response (136). Recently, our group has shown that PKR is activated (in the absence of virus) during obesity or lipid infusion in mice (36). Interestingly, PKR itself can orchestrate the activity of JNK and downregulate insulin signaling in metabolic cells, all from signals received via a HFD. Thus, the model derived from these examples is that nutrient overload induces pathogen sensors (**Figure 4**). The ability of PKR to interact with JNK and IKK as well as insulin signaling components and translational control through eIF2α also leads us to postulate that such complexes may represent metaflammasomes and may in fact be the recognition mechanisms for metabolic signals that trigger inflammation. Under regular conditions, the level of nutrients pouring into the system is low enough that only normal metabolic pathways are engaged and fidelity is ensured. However, upon overfeeding, the organism is exposed to high nutrient levels, which begin to directly activate pathogen-sensing molecules or pathways within the cells. This spillover of signals may even reach a third level as immune cells are activated and coordinate a multilayer response within the tissue, effectively blocking nutrient-induced anabolic activity.

Signals to Inflammatory Pathways

Evidence for the direct engagement of nutrients with pathogen or immune sensors is still lacking, but this remains one of the most fascinating areas of obesity research. An important future area in this respect is the systematic characterization of nutrients for their ability to directly engage innate immune responses through pathogen sensors or other mechanisms. Such platforms could give rise to groundbreaking insights regarding the health effects and underlying mechanistic actions of

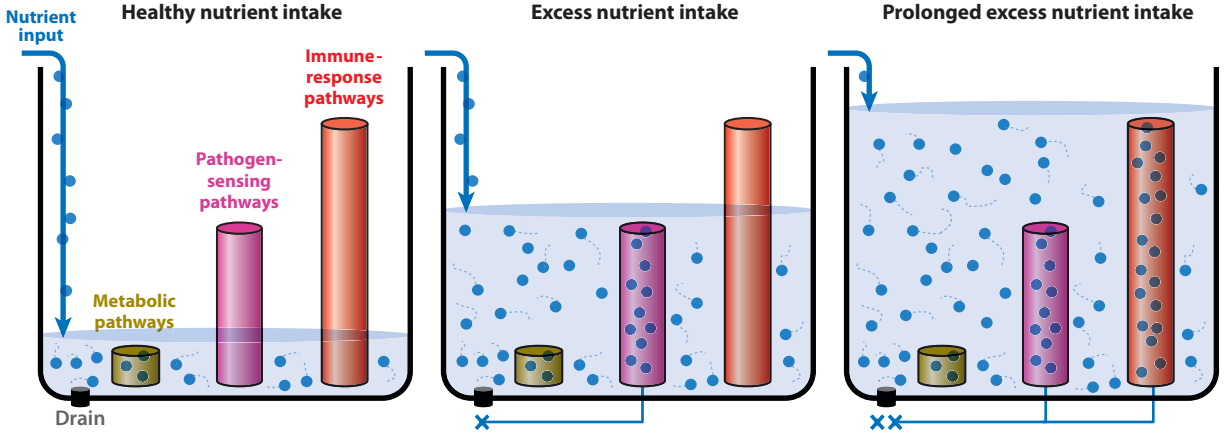

Figure 4

Overload of nutrient signals spills from metabolic pathways to immune-response pathways. Nutrient input under normal or healthy conditions should engage metabolic pathways within the cells, leaving immune-response pathways inactive. With increased nutrient intake, the levels of nutrients flooding the system may rise enough that the overflow stimulates pathogen-sensing pathways. Because these pathways recognize biological molecules (such as specific fatty acids), nutrient moieties in excess may also be able to activate such sensors. Once the immune sensors are activated, they may be antagonistic to the metabolic pathways, in effect blocking the drain of nutrient metabolism. If the nutrient excess persists to an extreme state, immune-response pathways of the professional immune cells may also be activated. The involvement of these pathways will intensify the inhibition of metabolic pathways and contribute to the backlog of nutrients in the system.

UPR: unfolded protein response

nutrients. For example, is there a nutrient that engages the TLR system? If so, at what concentration does the interaction take place? As mentioned above, the biological targets and actions of the overwhelming majority of nutrients, exogenous or endogenous, remain unknown. The concept of a nutrient-induced immune response provides an opportunity to approach a small but tractable portion of this vast question.

To date, studies in cultured cells have identified several candidates for inducers of metabolic inflammation. As implicated above, free fatty acids and especially saturated free fatty acids can activate inflammatory signaling in various cell types (137, 138). In addition, high glucose, hypoxia, and cell damage and death have all been proposed as initiators of inflammation during obesity (139, 140), often in combination. For example, one scenario may be that as the obese adipocyte expands, it reaches a mechanical limit to its storage capacity. The tissue may be less vascularized due to expansion, and the cell's stress response and perhaps even death response occur, releasing cytokines and excess fatty acids. These in turn are sensed by inflammatory kinases (such as JNK, PKR or IKK), the inflammasome, or TLRs, and an inflammatory cascade begins. There may also be specialized signaling complexes, metaflammasomes, that are organized by sensing molecules such as PKR and that coordinate the responses based on the nature and level of nutrient exposure. Such PKR complexes could also be integrating organelle function with metabolic and inflammatory outcomes (see below), and exploring these intriguing possibilities requires further work.

Organelle Stress

A key contributor to metabolic deterioration and the inflammatory response that deserves discussion is organelle dysfunction of the metabolic cells. Before we arrive at a single cytokine or free fatty acid inducer, we should consider that, in response to nutrient excess, the cell experiences functional stress that then generates an inflammatory response. For instance, we know that, compared with lean tissues, obese liver and adipose display increased levels of endoplasmic reticulum (ER) stress (141). As the ER is the primary site of protein folding in the cell, ER stress is measured by the activation of the unfolded protein response (UPR), which is driven by three main transmembrane sensors that reside on the ER, namely PERK (PKR-like eukaryotic initiation factor 2α kinase), IRE-1 (inositol-requiring enzyme 1), and ATF-6 (activating transcription factor 6) (reviewed in 142). Briefly, PERK, which possesses a kinase domain, inhibits general protein translation through phosphorylation of eIF2α, leading to alternative translation of ATF-4 and its downstream targets. IRE-1, a transmembrane protein that has kinase and endoribonuclease activities, cleaves the mRNA of the transcription factor XBP1 (X-box-binding protein 1), resulting in translation of an activated form of XBP1 responsible for upregulation of many chaperone genes. Finally, ATF-6 is a transcription factor that resides on the ER membrane and is cleaved in response to ER stress, producing an active factor that translocates to the nucleus and upregulates transcription of chaperone genes. The goal of activating the three arms of the UPR is to restore ER homeostasis by halting protein synthesis, increasing degradation of proteins from the ER, and increasing the level of chaperone proteins to assist in protein folding. If proper ER function cannot be achieved or if the stress continues, the UPR may also initiate apoptotic pathways. For in-depth discussion of this response and its effects on metabolism, we direct the reader to a recent review (66).

Interestingly, there are many connections between the UPR and inflammatory signaling pathways (**Figure 5**). First, chemical agents that target the UPR such as tunicamycin and thapsigargin lead to the induction of inflammatory kinases and the production of an array of inflammatory genes including *Il6*, *CXCL8*, *CCL2*, or *Tnfa* (143, 144). ER stress can also be a source of the production of oxidative stress or apoptosis, processes that themselves can lead to inflammation (145). Investigations into the mechanism behind this effect revealed that

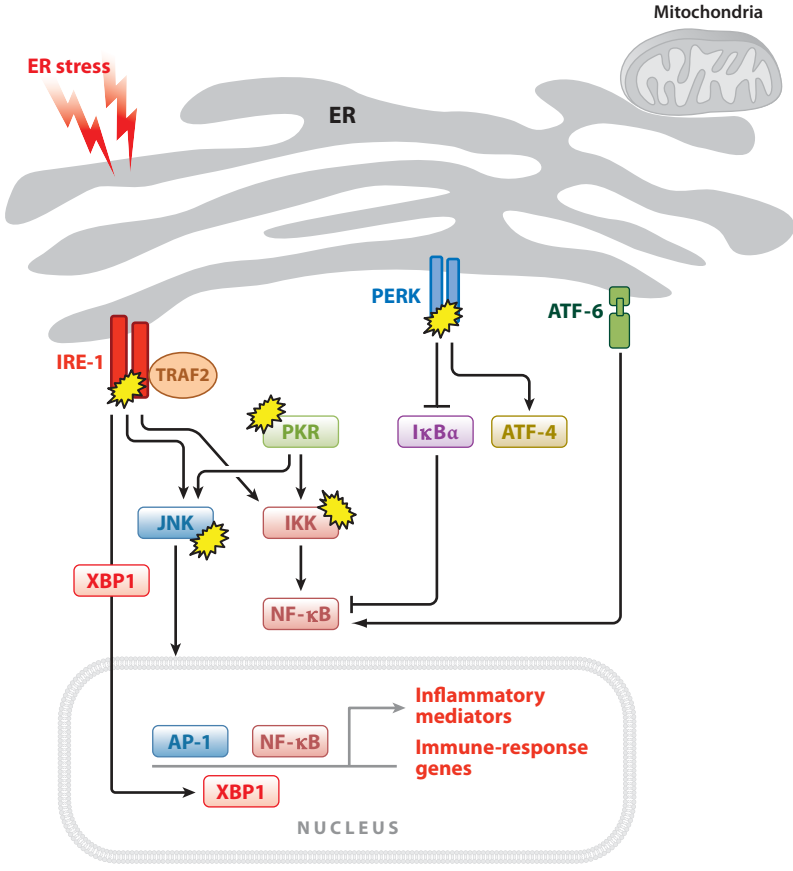

Figure 5

Endoplasmic reticulum (ER) stress pathways leading to inflammation. The three branches of the ER's unfolded protein response have all been implicated in the cellular inflammatory response. IRE-1 utilizes its kinase domain in association with TRAF2 to activate the inflammatory kinases JNK and IKK, leading to upregulation of inflammatory mediators via the transcription factors AP-1 and NF-κB, respectively. IRE-1 splicing of XBP1 mRNA also results in inflammatory consequences, as XBP1 has been shown to regulate inflammatory cytokine induction and immune responses in various cell types, especially macrophages. PERK activation leads to decreased translation of IκBα, an inhibitor of NF-κB signaling, thereby augmenting NF-κB transcriptional activity. In addition, PERK activation mediates ATF-4 translation, and ATF-4 was shown to regulate inflammatory cytokine induction, although the mechanism remains unknown. PKR is also activated by ER stress and contributes to JNK and IKK activation. Finally, ATF-6 has also been shown to increase NF-κB transcriptional activity. All of these pathways are linked to metabolic regulation, as discussed in the text. (Abbreviations: AP-1, activator protein-1; ATF-4/6, activating transcription factor 4/6; IKK, inhibitor of κ kinase; IRE-1, inositol-requiring enzyme 1; JNK, c-jun N-terminal kinase; PERK, PKR-like eukaryotic initiation factor 2α kinase; PKR, protein kinase R; TRAF2, TNF receptor-associated factor 2; XBP1, X-box-binding protein 1.)

IRE-1, through its kinase domain and interaction with TRAF2 (TNF receptor-associated factor 2), can activate both JNK and IKK, leading to increased expression of inflammatory cytokines (144, 146). In addition, PERK activation can also lead to enhanced NF-κB signaling. PERK-mediated inhibition of protein translation leads to decreased translation of IκBα (a negative regulator of IKK and NF-κB signaling) and results in greater activation of

NF-κB and the expression of its proinflammatory target genes *Tnfa* and *Il6* (147–149). ER stress can also activate PKR, itself an eIF2α kinase (36). Interestingly, PKR is required for full JNK activation in response to ER stress and also augments NF-κB signaling during inflammation, suggesting a central role for PKR in integrating organelle stress to inflammatory responses (36, 150). The UPR transcription factor ATF-6 has also been shown to increase NF-κB signaling (151), whereas ATF-4 and XBP1 have been implicated in the induction of inflammatory cytokines during UPR activation in various cell types (143, 152, 153). XBP1 in particular is necessary for a proper host response to pathogens in the induction of inflammatory cytokines, as evidenced by studies in *Caenorhabditis elegans* and in murine macrophages in vivo (153–155), suggesting a conserved mechanism whereby the ER and its UPR are intimately connected with host-cell defense. Finally, many of the above listed triggers (saturated free fatty acids, hypoxia, high glucose) that can induce inflammatory signaling also induce ER stress (145).

How do we bring these relationships to bear in the context of obesity? Given that obese animals exhibit an increased UPR activation compared with lean controls, the various arms of the UPR may be sources of the inflammatory response in the specialized metabolic cells. Of note, a mouse model bearing genetic haploinsufficiency of XBP1 exhibited an aggravated UPR response compared with wild-type mice, and intriguingly, these mice also displayed increased body weight, insulin resistance, and glucose intolerance (141). We suggest that organelle dysfunction in response to nutrient overload causes a unique inflammatory response in the metabolic cells that then leads to inhibition of insulin signaling, beginning the pathological process of insulin resistance and homeostatic dysfunction. This is a hypothesis, and as yet no definitive study exists that connects the UPR to inflammation during the onset of obesity and its complications. Although activation of inflammatory kinases such as JNK and IKKβ are clearly linked to ER stress, future study in this area will reveal the importance of the UPR as a mechanism of metabolic inflammation.

ARE ANTI-INFLAMMATORY THERAPIES IMPORTANT TO OBESITY TREATMENT?

As described above, inflammation causes adverse metabolic consequences in every tissue investigated thus far. This striking finding naturally leads to the question of therapeutic intervention by modulation of inflammatory cascades. Will inhibition of obesity-induced inflammation lead to beneficial effects on organismal metabolism? If so, what are the optimal strategies to design such agents? Studies from the literature targeting actual inflammatory molecules in metabolic disease are few in number. In one study, blocking TNF-α in a small group of obese T2D patients decreased plasma levels of inflammatory markers but did not alter systemic insulin sensitivity (156). However, treatment of insulin-resistant rheumatoid arthritic patients with TNF-α antibody did improve insulin resistance (157), indicating that additional and more detailed studies with these agents in a larger number of subjects are required to form a conclusion. One promising very recent study also reported that treatment of obese T2D patients with etanercept, a TNF-α antagonist, resulted in reduced blood glucose and increased high molecular weight adiponectin levels (158). Another important study using recombinant IL-1 receptor antagonist also yielded positive metabolic results such as improved glycemia and increased β cell secretion of insulin (159). These studies are important as direct proof-of-principle that addressing the inflammatory component of obesity results in improved insulin sensitivity in humans. However, whether blocking the action of a single cytokine is a feasible and sufficiently potent intervention in obesity and T2D remains a subject of ongoing debate.

Targets to reduce obesity-associated inflammation may also include the kinases or pathogen-sensing pathways described above,

and it is likely that such interventions may prove to be more effective. In obese mice, administration of either synthetic or peptide JNK inhibitors, interfering RNAs, or dominant-negative approaches led to significant metabolic improvements, including increased glucose tolerance and recovery of insulin sensitivity (90, 92, 93, 160). The efficacy of the JNK-targeted molecules in humans remains to be evaluated. However, it appears that preventing activation of these upstream kinases (which influence a program of mediators) would be far more effective than interfering with individual classic inflammatory mediators known at this time. Support for such an idea also comes from the extensive studies performed with the anti-inflammatory drug family of salicylates, hypothesized to decrease inflammation through inhibition of IKK activity. Multiple independent studies have supported the finding that treatment of T2D patients with salsalate or aspirin lowers systemic inflammation, improves glycemia, lowers blood lipid levels, and increases circulating adiponectin (161–163). Although the precise target of salsalates remains a subject of discussion, these agents clearly prevent inflammation in a broad manner and diminish the pathological activation of multiple signaling networks that are critical in metabolic deterioration.

Cell-based immunotherapy also presents itself as an option, achieved through manipulation of the immune cells themselves. As discussed above, elimination or inhibition of various cell types such as $CD11c^+$ immune cells, various populations of T cells, and even mast cells in obese mouse models have yielded beneficial metabolic effects (45, 47–49, 86). This area is just beginning to develop and may hold promise in obesity-related disease. Again, in this context it will be important to understand the metabolic signals that give rise to activation of these immune effectors and prevent their action specifically, rather than interfering with the entire immunological cell population.

Finally, agents that target the original signals to inflammation in obesity are also under investigation. For example, ameliorating ER stress in the specialized metabolic cell may cut off the source of inflammatory signals and restore insulin sensitivity. Indeed, obese mice treated with two different chemical chaperones exhibited reduced ER stress in metabolic tissues and substantial increases in glucose tolerance and insulin sensitivity, accompanied by a decrease in JNK activity (164). One of these molecules has also been tested in obese humans and in a small clinical trial demonstrated promising insulin-sensitizing activity (165). Thus, amelioration of ER stress carries strong potential for therapeutic intervention.

Restoring natural or endogenous anti-inflammatory molecules to metabolic cells may also be beneficial. The best example of this is PPARγ activation in adipose tissue. PPARγ is a transcription factor that controls adipogenesis and adipocyte-specific functions. The group of compounds known as thiazolidienes (TZDs) is a potent agonist of PPARγ already in clinical use as insulin sensitizers (although their use is controversial). TZDs not only activate PPARγ and restore lipogenic function to adipocytes, but also possess anti-inflammatory properties (74, 166, 167). In addition, one PPARγ target, adiponectin, is an adipokine that acts as an endogenous anti-inflammatory molecule. Adiponectin can upregulate IL-10 expression in macrophages and leukocytes, resulting in potent anti-inflammatory activity (168, 169). TZDs as a therapeutic agent increase adiponectin expression and possess anti-inflammatory activities. Whether this is the primary mechanism of improving insulin sensitivity is not yet known. Adiponectin itself as a treatment for T2D has not been investigated in humans, although in mice delivery of recombinant protein reduces the production of inflammatory cytokines such as TNF-α, lowers blood glucose levels, relieves fatty liver, and may reduce atherosclerosis (170–173). In obese humans, one recent study showed that blocking TNF-α increased the level of biologically active, high molecular weight, adiponectin levels (158).

A new area of promising research in therapeutic approaches against obesity

and metabolic disease is the use of anti-inflammatory nutrients provided through diet. The most studied example may be the omega-3 polyunsaturated fatty acids (n-3 PUFAs). This fatty acid in particular possesses anti-inflammatory properties via its metabolites EPA and DHA and has already been shown to ameliorate inflammatory diseases such as cardiovascular disease, atherosclerosis, and inflammatory bowel disease (174). Mouse studies supplementing HFDs with n-3 PUFAs reveal decreased expression of inflammatory cytokines and macrophage infiltration in adipose tissue and increased insulin sensitivity in liver and muscle (175, 176). In humans, there are few data investigating the effects of n-3 PUFAs in obesity and T2D. In a study of T2D women, n-3 PUFA intake was associated with decreased risk of developing cardiovascular disease (177), and a second study reported decreased triglyceride levels in T2D patients supplemented with n-3 PUFAs (178). Additional studies in this area will be important to assess the benefits or lack thereof of n-3 PUFAs on obese pathologies. Interestingly, our lab recently identified a lipokine from adipose tissue, C16:1n7-palmitoleate, that possesses potent insulin-sensitizing properties, including stimulation of glucose removal by muscle and inhibition of lipogenic pathways in the liver (179). This lipokine can also neutralize some of the detrimental and inflammatory effects of saturated fatty acids and may contribute to regulation of metabolically triggered inflammatory responses (179). As palmitoleate is a naturally occurring lipid, dietary supplement during metabolic disease is an attractive therapeutic option to be explored. In fact, recent studies have found significant association between palmitoleate levels and metabolic disease in humans, providing further support for such possibilities (180–181). Thus, the difference between inflammatory and anti-inflammatory nutrients remains a fascinating area of future work, including the identification of other nutrients with such anti-inflammatory properties and the effects these may have on dysfunctional tissues.

Discussion of anti-inflammatory therapy raises the fundamental question of whether we should inhibit inflammation in the first place. Inflammation is a host response to danger, usually in the form of a pathogen or injury, which is necessary for wound repair and survival. Removing this signal altogether before the threat is resolved may leave the system vulnerable to continuing damage or subsequent exposures. We assume that in obesity the inflammation is caused by nutrient signals, and therefore inhibition of inflammatory mediators will not remove the troublesome excess nutrients or the accompanying organelle dysfunction that is related to the metabolic signals. However, if inflammation is regulating how the cells react to the excess nutrients and therefore exacerbating insulin resistance, inhibition may still be helpful. Ultimately, the most effective strategies should address the root causes as well the inflammatory consequences of chronic metabolic disease. The strategies should focus on the right mechanistic bases or targets without compromising the immune response in general.

In conclusion, we propose that in obesity immune and metabolic pathways unite to affect cell function. Therefore, anti-inflammatory therapies are valuable in that they compromise the engagement of these two pathways and may effectually take out one of the eyes of the monster that is driving the insulin resistance of obesity and its related pathologies.

SUMMARY POINTS

1. Obesity-induced inflammation may be best described as metaflammation: a chronic, low-grade inflammatory response initiated by excess nutrients in metabolic cells. The inflammatory signaling conducted by the metabolic cell eventually causes activation of specialized immune cells and leads to an unresolved inflammatory response within the tissue.

2. Metaflammation in general has inhibitory effects on insulin action through the inflammatory kinases JNK, IKK, and PKR in metabolic tissues and disrupts nutrient and energy metabolism through these or other mechanisms.
3. Obesity may induce metaflammation when nutrient excess engages pathogen sensing either through physiological nutrient-induced stress taken to extremes or through a dose-dependent loss of specificity that activates immune-response pathways.
4. Therapeutic interventions to inhibit inflammatory pathways in obesity are showing beneficial effects on insulin sensitivity in mouse models and human trials.

FUTURE ISSUES

1. Is there such a thing as inflammatory versus noninflammatory nutrients? How can specific nutrients that trigger metaflammation be identified?
2. Is there a metaflammasome(s) where multiple endogenous and exogenous metabolic signals are received and conveyed into inflammatory signaling complexes and networks?
3. Can metabolic health be preserved or recovered despite inflammation by alternative interventions or is it mandatory to dampen metaflammation?
4. Are there any beneficial effects from the inflammation associated with obesity?

DISCLOSURE STATEMENT

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Errata

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