

Regulation of Nutrient Metabolism and Inflammation

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Abstract Metabolic and immune-related pathways intersect at numerous levels. Their common regulation is effectuated by several hormonal signaling routes that involve specific nuclear hormone receptors and adipokines. Glucocorticoids and leptin are hormones that play a key role in coordinating energy metabolism and food-seeking behavior during energy deficiency as does the nuclear hormone receptor Peroxisome Proliferator Activated Receptor α (PPAR α). Importantly, the glucocorticoid, leptin, and PPAR α signaling routes share a profound role in governing inflammation and other immune-related processes. Using specific examples, this chapter aims at illustrating the interplay between metabolism and immunity/inflammation by discussing common endocrine and transcriptional regulators of metabolism and inflammation and by highlighting the interaction between macrophages and metabolically active cells in liver and adipose tissue. Convergence of metabolic and immune signaling is likely at least partially driven by the evolutionary need during times of food insufficiency to minimize loss of energy to processes that are temporarily nonessential to the survival of the species.

1 General Introduction

The present-day abundance of highly palatable foods combined with the astounding number of people suffering from diseases of affluence makes it hard to imagine that mankind evolved under less favorable nutritional circumstances. Most of our ancestors had to cope with repeated and prolonged periods of caloric insufficiency or even starvation, especially during winter or when traveling long distances. In fact, even in western societies, general food security was only attained two to

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three generations ago, and undernutrition is still common in many parts of the world. As a consequence, caloric insufficiency and starvation have served as key evolutionary pressures throughout history that have shaped energy metabolism in humans and determined our metabolic response to the current food excess (Prentice et al. 2008).

In addition to food insufficiency, our ancestors were subjected to numerous infectious challenges, ranging from pathogenic bacteria to viruses and parasites, which triggered the evolution of a highly complex immune defense system that is able to ward off all but the most formidable pathogens. But although an efficiently working immune system was critical for the long-term survival of the human species, it was likely of lesser importance during period of energy shortage, when energy conservation must prevail. In *Drosophila*, immunodeficient mutant flies that do not have to invest into immunological maintenance were found to have an extended lifespan under starvation conditions compared to wild-type flies, whereas the opposite occurred under fed conditions (Valtonen et al. 2010). The pressure to conserve energy may explain why starvation and undernutrition can wreak havoc on the immune system and give rise to general immunosuppression.

But the interaction between metabolism and immunity is not just a one-way street. Indeed, infections are well recognized to have a major impact on nutrient metabolism, increasing energy requirements and, depending on the severity of infection, cause significant protein catabolism and cachexia (Goldstein and Elwyn 1989). Given the important links between metabolism and immunity, it comes as no surprise that the regulatory mechanisms that govern metabolism and immunity intersect at numerous levels. In fact, many of the endocrine factors that are responsible for coordinating metabolic pathways also directly govern inflammatory routes. Conversely, a growing list of circulating inflammatory and immune modulators has been shown to impact metabolic pathways. This chapter is aimed at illustrating the interplay between metabolism and immunity/inflammation by discussing common endocrine and transcriptional regulators of metabolism and inflammation and by highlighting the interaction between macrophages and metabolically active cells in liver and adipose tissue. The chapter does not aim to be exhaustive but rather uses specific examples to emphasize the importance of cross-talk between metabolic and immune regulation in response to disturbances of homeostasis.

2 Common Endocrine and Transcriptional Regulators of Metabolism and Inflammation

2.1 Regulation of Metabolism and Immunity by Leptin

Although energy conservation is of prime importance to any organism at risk of experiencing major food scarcity to assure the survival of the species, the need to save energy becomes especially important during actual episodes of caloric insufficiency.

Under those circumstances, limiting energy usage and shifting metabolism toward oxidation of stored nutrients take precedence, while nonessential processes such as the immune response become deprioritized. The parallel changes in energy metabolism and the immune system are effectuated by a number of hormonal systems, three of which are discussed in more detail below.

One major hormone that aptly embodies the convergence of metabolic and immunological regulation is leptin (Fig. 1). Leptin is a 16-kDa protein predominantly secreted by adipocytes (Zhang et al. 1994). Consequently, plasma leptin levels are positively correlated with body fat mass. Moreover, plasma leptin levels acutely decrease during fasting, which via the leptin receptor OB-Rb triggers neuronal circuits in the arcuate nucleus of the hypothalamus (Friedman and Halaas 1998). Specifically, leptin increases production of satiety-inducing signals α Melanocyte-Stimulating Hormone and Cocaine- and Amphetamine-Regulated Transcript and decreases production of hunger-provoking peptides Neuropeptide Y and Agouti-Related Protein. Absence of leptin causes severe hyperphagia in mouse and humans, which combined with reduced energy expenditure leads to morbid obesity in both species (Farooqi and O'Rahilly 2009). Leptin increases energy expenditure in part by stimulating uncoupling in white and brown adipose tissue (Commings et al. 1999), as well as via increased spontaneous activity (Pellemounter et al. 1995). The metabolic effects of leptin appear to be mediated by Adenosine MonoPhosphate-dependent kinase and by the signal transduction cascades that are also involved in the immune-modulating actions of leptin (Minokoshi et al. 2002).

Illustrating the close ties with immune function, the receptor for leptin is a member of the class I cytokine receptor family and is homologous to gp-130, the signaling transducing subunit of IL-6 family cytokines (Tartaglia et al. 1995). In addition to the hypothalamus, the leptin receptor can be found on numerous types of immune cells including subpopulations of T cells, B cells, dendritic cells, monocytes, neutrophils, macrophages, and natural killer cells (Fig. 1) (Gainsford

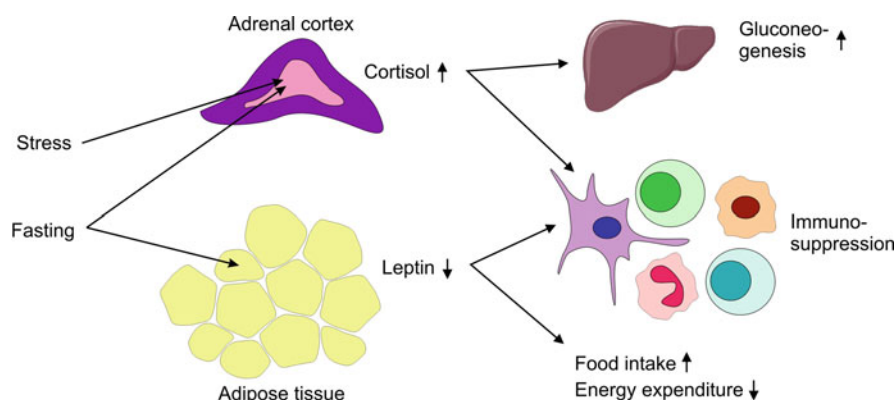


Fig. 1 Importance of glucocorticoid and leptin signaling in coordinating metabolic and immune-related responses during stress and fasting

et al. 1996). Binding of leptin to the receptor and subsequent activation of downstream effector JAK2 causes phosphorylation and concurrent activation of STAT transcription factors, which are also targeted by other cytokines (Ghilardi et al. 1996). STAT proteins play a central role in the immune response by regulating the expression of numerous cytokines and other immunologically relevant genes. Phosphorylated JAK2 also activates other pathways including Mitogen-Activated Protein kinase/Extracellular signal-Regulated Kinase (ERK) and Phosphatidylinositol 3-Kinase/Protein Kinase B. The latter pathway represents a key signaling cascade that mediates effects of various proinflammatory cytokines and bacterial and viral stimuli in a variety of immune cells. Through these mechanisms, leptin targets both innate and acquired immunity. With respect to innate immunity, leptin has been shown to enhance phagocytosis by monocyte/macrophages. Moreover, leptin stimulates secretion of proinflammatory mediators of the acute-phase response and the expression of adhesion molecules (La Cava and Matarese 2004). With respect to acquired immunity, a wealth of data is available showing that leptin impacts diverse aspects of T cell-mediated immunity, as first revealed by the higher number of circulating regulatory T cells in mice lacking leptin. Strikingly, the alterations in immune function in mice lacking leptin resemble the state of immunodeficiency observed with caloric insufficiency and starvation (Howard et al. 1999), suggesting that decreased leptin is a key mediator of the immune suppression of malnutrition (Lord et al. 1998).

Leptin can thus be regarded as a primordial hunger/satiety hormone that responds to acute and chronic energy shortage by promoting food-seeking behavior and energy conservation. It is likely that its immune-modulating function was acquired during the course of evolution as a mechanism to minimize energy losses via redundant processes. The alternative scenario in which leptin initially functioned as immune modulator that later adopted the ability to govern food intake seems much less plausible. Interestingly, similar convergence of metabolic and immune regulation is found for other adipokines such as adiponectin and resistin (Trayhurn and Wood 2004).

2.2 Regulation of Metabolism and Immunity by Glucocorticoids

Another group of hormones that have a central role in regulation of metabolism and inflammation are the glucocorticoids (Fig. 1). Befitting their name, glucocorticoids, including its principal representative cortisol, stimulate processes that collectively serve to maintain blood sugar levels during fasting, thus opposing the action of insulin. Moreover, glucocorticoids cause release of stored energy via stimulation of adipose tissue lipolysis and muscle proteolysis. As a consequence, pathologically increased circulating cortisol concentration give rise to dysmetabolic features such central obesity, insulin resistance, and dyslipidemia (Mattsson and Olsson 2007). Apart from its role in nutrient metabolism, glucocorticoids

have a major impact on inflammatory and immune-related processes (Cupps and Fauci 1982). Oral glucocorticoids represent the most widely used treatment for a great variety of acute and chronic inflammatory disorders, including chronic obstructive pulmonary diseases, inflammatory skin disorders, and rheumatoid arthritis. At the cellular level, glucocorticoids inhibit the access of leukocytes to inflammatory sites, interfere with the functions of leukocytes, endothelial cells, and fibroblasts, and suppress the production and the effects of humoral factors involved in the inflammatory and immune response (Boumpas et al. 1993). The pleiotropic effects of glucocorticoids, which extend far beyond inflammation and metabolism and also include effects on fetal development, brain function, and bone formation, are reflected in the diverse genes and processes controlled by the glucocorticoid receptor (GR), a member of nuclear receptors superfamily (Beck et al. 2009). While normally residing in the cytosol, GR translocates into the nucleus upon binding of glucocorticoids. There, GR serves as transcriptional activator of distinct glucocorticoid-responsive target genes via direct DNA binding to GR-responsive elements (GRE), in conformance with the general mechanism of gene regulation by nuclear receptors. Absence of GR in liver leads to fasting hypoglycemia, illustrating the importance of GR in maintaining blood glucose concentrations via stimulation of hepatic gluconeogenesis and its key targets phosphoenolpyruvate carboxykinase and glucose 6-phosphatase (Imai et al. 1990; Opherk et al. 2004). With respect to lipid metabolism, glucocorticoids have been shown to raise plasma-free fatty acid levels, reflecting increased whole body lipolysis, yet promote central fat deposition (Macfarlane et al. 2008).

Whereas glucocorticoids influence nutrient metabolism primarily by directly stimulating gene transcription, the anti-inflammatory and immune-suppressive effects of activated GR are mainly mediated by altering the activity of other DNA-bound transcription factors via a mechanism that does not require DNA binding of GR referred to as transrepression. Indeed, using mice with a mutation in the GR gene that prevents transcriptional activation of classical GRE-regulated genes, it was shown that repression of inflammatory responses by glucocorticoids is independent of GR binding to DNA (Reichardt et al. 2001). Many transcription factors are targeted for transrepression by GR, including NF- κ B, AP-1, NF-AT, T-bet, GATA-3, and IRF3, thereby explaining the diverse effects of glucocorticoids on inflammation and immunity observed in a variety of different cell types. GR represses NF- κ B transcriptional activity by physically interacting with the p65 subunit, preventing it from gaining access to DNA. Additionally, GR and NF- κ B may compete for mutual cofactors required for transcriptional activation (Smoak and Cidlowski 2004).

Similar to the situation for leptin, the question can be raised why regulation of metabolism and inflammation is effectuated by a single hormone via a single receptor. Glucocorticoids allow the body to respond adequately to physical or emotional stress via adjustments in the metabolic flux to support those processes that are essential for the immediate survival of the organism. Although this may be the evolutionary basis for the comprehensive properties of GR, it seems plausible

that additional immune-modulating functions of GR have evolved that are not strictly connected to the starvation response.

2.3 Regulation of Metabolism and Immunity by PPAR α

Analogous to GR, another nuclear receptor governing both metabolic and immune-related processes is PPAR α , which serves as the molecular target for hypolipidemic fibrate drugs. PPAR α can be considered the master regulator of fatty acid metabolism in liver. It is especially active in the fasted state, giving rise to induction of numerous genes involved in fatty acid uptake, fatty acid oxidation, triglyceride synthesis and hydrolysis, and other fatty acid metabolic pathways (Kersten et al. 2000). Additionally, activation of PPAR α has a major impact on inflammatory processes in liver, which is mainly accomplished via downregulation of gene expression by interfering with specific inflammatory signaling pathways, leading to attenuation of cytokine-induced production of acute-phase proteins such as fibrinogen, haptoglobin, and serum amyloid (Gervois et al. 2004; Mansouri et al. 2008). Similarly, the presence of PPAR α protects against obesity-induced hepatic inflammation (Stienstra et al. 2007). With respect to the mechanisms involved, it has been shown that activated PPAR α binds to c-Jun and the p65 subunit of NF- κ B, thereby inhibiting AP-1- and NF- κ B-mediated signaling (Delerive et al. 2001). Recent high throughput DNA binding studies of PPAR α via ChIP on CHIP revealed that PPAR α activation in hepatocytes causes the dissociation of STAT transcription factors from the DNA, resulting in downregulation of gene expression (van der Meer et al. 2010). As mentioned above, STATs are also targeted by leptin, suggesting potential synergy between the PPAR α and leptin pathways to suppress STAT-dependent inflammatory signaling during fasting. In general, the mechanisms underlying the anti-inflammatory effects of PPAR α are reminiscent to those of GR, and indeed cooperation between anti-inflammatory activities of the two receptors has been demonstrated (Bougarne et al. 2009).

Although synthetic fibrates potentially activate PPAR α to cause suppression of inflammation in liver and the vascular wall, it should be stressed that the receptor did not evolve as a drug target but rather as a lipid target with a preference for long chain unsaturated fatty acids and its derivatives. Numerous studies using a variety of biochemical techniques have firmly corroborated direct physical association between fatty acids and PPARs and have established fatty acids as bona fide PPAR ligands (Jump et al. 2005). Recently, it was shown that the effects of dietary unsaturated fatty acids on hepatic gene expression are almost entirely mediated by PPAR α (Sanderson et al. 2008). PPAR α may thus serve as mediator of the inflammatory activity of dietary fatty acids and thereby link diet composition to regulation of the inflammatory response in liver. A similar scenario can be envisioned for PPAR β/δ and PPAR γ , which also function as lipid sensors and have major anti-inflammatory properties in several cells and tissues (Bishop-Bailey and Bystrom 2009; Straus and Glass 2007).

3 Interaction Between Macrophages and Metabolically Active Cells in Liver and Adipose Tissue

While there are thus numerous examples for coordinated regulation of metabolism and inflammation/immunity as part of normal homeostasis, cross-talk between metabolism and inflammation can also be triggered by specific disease conditions representing perturbations of homeostasis. Indeed, deviations of metabolic homeostasis as in obesity elicits marked changes in inflammatory pathways, and vice versa a strong inflammatory response can have a major impact on numerous metabolic processes, including lipoprotein metabolism, insulin signaling, and energy expenditure. Below, it is discussed how in the state of obesity interactions exist in liver and adipose tissue between macrophages and the metabolically active main cell types, which importantly contributes to some of the complications of obesity.

3.1 Role of Adipose Tissue Macrophages in Obesity

Contradicting the widespread connotation of body fat with inactivity, over the last two decades, it has become evident that the adipose tissue is anything but inactive and represents a highly dynamic organ that rapidly adapts to changes in nutritional status via alterations in secretory profile, blood flow, and cell composition. Traditionally viewed as an organ composed almost entirely of adipocytes complemented with some vascular cells and fibroblasts, it is now commonly accepted that numerous types of leukocytes are present in between the adipocytes (Anderson et al. 2010). This pool of white blood cells expands dramatically upon obesity, creating an optimal forum for exchange of signals between immune cells and metabolically active cells. Most of the attention has been focused on macrophages, which were shown to infiltrate the adipose tissue and account for production of specific cytokines (Weisberg et al. 2003; Xu et al. 2003). In addition, adipocytes themselves are capable of secreting a variety of proteins, including TNF α and leptin (Hotamisligil et al. 1993; Zhang et al. 1994). During adipose tissue expansion, changes in the secretory profile of adipocytes and incoming and resident leukocytes lead to altered release of numerous (adipo)cytokine. Accordingly, obesity is nowadays considered a state of chronic low-grade inflammation, illustrating the intimate relationship between metabolism and inflammation.

How obesity leads to enhanced macrophage abundance is not clear but a role for adipocyte cell death, hypoxia, and local insulin resistance has been surmised, the latter being possibly related to ER stress, ROS formation, and mitochondrial dysfunction (Lee et al. 2009). A number of chemotactic signals including Monocyte Chemoattractant Protein 1 likely contribute to macrophage recruitment in adipose tissue (Kamei et al. 2006; Kanda et al. 2006; Yu et al. 2006). Recently, it was shown that T cells are also actively regulated in adipose tissue and contribute to obesity-induced inflammation (Feuerer et al. 2009; Nishimura et al. 2009; Winer et al. 2009).

Studies have also indicated that macrophages present within adipose tissue display pronounced heterogeneity and can roughly be separated into classically activated proinflammatory M1 macrophages and alternatively activated anti-inflammatory M2 macrophages. While adipose tissue of lean mice mainly contains M2 macrophages, diet-induced obesity was shown to specifically increase adipose abundance of M1 macrophages via recruitment from the circulation (Lumeng et al. 2008). The activation state of adipose tissue macrophages may in part be determined by T cells via specific T helper type 1 or T helper type 2 cytokines (Strissel et al. 2010). M1 macrophages are thought to contribute to development of insulin resistance in obese animals via production of proinflammatory cytokines, which negatively impact peripheral and hepatic insulin signaling. These effects are mediated by specific kinases such as Inhibitor of NF- κ B Kinase β (IKK β), c-Jun N-terminal Kinase (cJNK), ERK, mammalian Target Of Rapamycin (mTOR), and p70 ribosomal S6 protein Kinase (S6K) that cause phosphorylation of insulin receptor substrate 1 and 2 at specific serine residues, leading to their inactivation (Shoelson et al. 2007). Normally, binding of insulin to its receptor triggers phosphorylation of insulin receptor substrates at specific tyrosine residues, leading to their activation. In recent years, this so-called inflammatory hypothesis has gained acceptance as an at least partial explanation for the link between obesity and local and possibly systemic insulin resistance (Lee et al. 2009).

3.2 Cross-talk Between Hepatocytes and Kupffer Cells

The close proximity and the chemical interaction between leukocytes and metabolically active cells is not an exclusive phenomenon of the obese adipose tissue. The liver represents a unique system in which the metabolically relevant hepatocytes coexist with resident macrophages referred to as Kupffer cells (Fig. 2). Kupffer cells are derived from circulating monocytes that arise from bone marrow progenitors. Once in the liver, the cells differentiate to Kupffer cells and acquire the ability to perform various functions, including phagocytosis, antigen processing, and antigen presentation. Via the generation of different products, including cytokines, prostanooids, nitric oxide, and reactive oxygen intermediates, Kupffer cells influence the phenotypes of other immune cells and neighboring hepatocytes. Recent studies point to important cross-talk between Kupffer cells and hepatocytes in the regulation of lipid metabolism in the context of nonalcohol fatty liver disease (NAFLD). NAFLD represents the most common liver disorder in industrialized countries and is highly correlated with obesity. It is characterized by accumulation of fat in hepatocytes and can vary from the relatively benign hepatic steatosis to severe steatohepatitis, which might progress to end-stage liver diseases such as cirrhosis and liver cancer. Several studies (Huang et al. 2010; Neyrinck et al. 2009; Rivera et al. 2007; Stienstra et al. 2010), though not all (Clementi et al. 2009; Lanthier et al. 2009), found that when liver was depleted of Kupffer cells using clodronate liposomes or gadolinium chloride, hepatic lipid accumulation in mouse models of

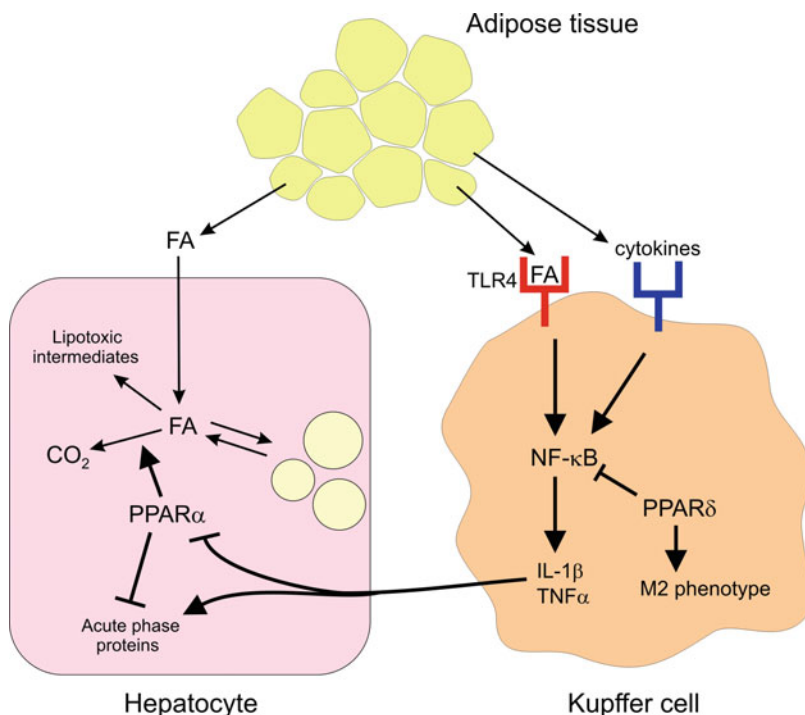


Fig. 2 Model for interactions between hepatocytes and Kupffer cells influencing lipid metabolism and inflammatory responses. *FA* fatty acids; *TLR4* Toll-like receptor 4

steatosis or steatohepatitis was reduced, leading to improved insulin sensitivity (Huang et al. 2010; Neyrinck et al. 2009). Kupffer cells may stimulate triglyceride storage and suppress fatty acid oxidation in hepatocytes via TNF α (Huang et al. 2010). Alternatively, a role for Kupffer cell-derived IL-1 β in promoting lipid accumulation via induction of Dgat2 expression or suppression of PPAR α -dependent regulation of hepatic fatty acid oxidation has been proposed (Fig. 2) (Miura et al. 2010; Stienstra et al. 2010). The specific impact of Kupffer cells on lipid metabolism in hepatocytes may depend on their polarization state and inflammatory status. A recent study provided compelling evidence that the transcription factor PPAR β/δ may stimulate fatty acid oxidation and thereby protect against hepatic steatosis by promoting a M2-like phenotype in Kupffer cells (Odegaard et al. 2008).

Conversely, altered lipid metabolism and lipid accumulation in the hepatocyte may affect Kupffer cell activity (Baffy 2009). It is well established that hepatic steatosis increases the risk for inflammatory complications leading to nonalcoholic steatohepatitis. First, the increased space occupied by fatty hepatocytes may lead to impaired sinusoidal perfusion and entrapment of leukocytes, thereby engaging Kupffer cells. Second, impaired fatty acid uptake in hepatocytes and/or elevated lipolysis may increase exposure of Kupffer cells to fatty acids, leading to modulation of inflammatory pathways via interaction with cell surface receptors such as Toll-like

receptor 4. Toll-like receptor 4 has been proposed as a relay system that mediates the proinflammatory effects of saturated fatty acids (Lee et al. 2001), although this concept has been challenged (Erridge and Samani 2009). Finally, excess lipids in hepatocytes may trigger lipotoxicity reflected by formation of reactive oxygen species, disturbances in cellular membrane fatty acid and phospholipid composition, and alterations of cholesterol content and ceramide signaling. These lipotoxic changes may cause hepatocellular damage and ultimately death, leading to activation of Kupffer cells (Trauner et al. 2010).

It is thus evident that throughout the various stages of NAFLD, signals traveling from Kupffer cells to hepatocytes and vice versa play a key role in determining the course of the disease. To what degree these mutual interactions between hepatocytes and Kupffer cells influence lipid metabolism under more physiological conditions will require further study.

4 Concluding Remarks

Over the past decade or so, metabolism and immunity have turned from vague acquaintances into best friends. Although it has been recognized for a long time that inflammatory conditions profoundly disturb metabolic regulation, the notion that metabolic diseases are often associated with marked changes in the immune system only gained acceptance more recently. The examples outlined above illustrate our rapidly growing insight into the molecular mechanisms that govern cross-talk between metabolic and immune-related signaling. These interconnections likely originated from the need of an organism to balance the energetic costs of immune responsiveness with its core mission of survival. It is expected that future research will further clarify specific mechanism of cross-talk between metabolic and immune regulation.

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