Molecular mechanism underlying nutritional control of inflammatory responses

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Abstract  Storage of excessive energy as triglycerides is a fundamental function of adipose tissue. Adipose tissue also secretes a number of hormones termed “adipocytokines” or “adipokines” in response to the systemic nutritional status, thereby constituting a feedback mechanism of metabolic homeostasis. In this regard, adipose tissue senses systemic nutritional conditions and regulates systemic metabolic homeostasis. During the past decade, there has been remarkable progress in the molecular mechanism underlying obesity-induced adipose tissue dysfunction. Accumulating evidence has suggested that a variety of stromal cells induce adipose tissue remodeling, which impairs adipose tissue function such as lipid storage and adipocytokine production, thereby leading to systemic metabolic derangements. Namely, chronic inflammation provides a molecular basis underlying obesity-induced adipose tissue dysfunction. In contrast, nutritional deprivation or malnutrition results in immune dysfunction, at least partly, through adipocytokine dysregulation. Thus, adipose tissue links nutritional conditions and inflammatory responses.

Keywords : metabolic syndrome, obesity, adipocytes, macrophages, chronic inflammation

Introduction  During the past few decades, modernization of our daily life, including a sedentary lifestyle and high-calorie diet, has escalated an obesity pandemic, together with obesity-related complications such as diabetes and cardiovascular disease. Obesity is now considered an inflammatory disease as well as a metabolic disease. There are numerous studies with regard to how excessive energy intake and nutritional imbalance induce chronic inflammation, which leads to impaired metabolic homeostasis. In this regard, adipose tissue is a key organ that senses nutritional conditions in our body and regulates inflammatory responses. Storage of excessive energy as triglyceride is a fundamental function of adipose tissue. Adipose tissue also secretes a number of hormones termed “adipocytokines” or “adipokines” in response to the systemic nutritional status, thereby constituting a feedback mechanism of metabolic homeostasis. Accumulating evidence has suggested that chronic inflammation provides a molecular basis underlying obesity-induced adipose tissue dysfunction. In contrast, nutritional deprivation or malnutrition suppresses immune function, thereby conferring higher susceptibility to infectious diseases. Indeed, nutritional deprivation induces atrophy of lymphoid tissues such as in the thymus and spleen, and decreases the number of circulating lymphocytes. As a molecular mechanism linking nutritional conditions and immune function, leptin, a major adipocytokine, plays an important role. Given that the nutritional status controls inflammation or immune function and vice versa, it is important to know how adipose tissue regulates these processes. In this review article, we will mainly focus on the role of adipose tissue in nutritional control of inflammatory responses.

Obesity-induced adipose tissue remodeling  In addition to lipid-laden mature adipocytes, a variety of stromal cells are included in adipose tissue such as preadipocytes, endothelial cells, fibroblasts, and immune cells, which are referred to as the stromal-vascular fraction. Interestingly, obesity induces drastic histological changes in adipose tissue termed “adipose tissue remodeling”: adipocyte hypertrophy and hyperplasia along with immune cell infiltration, angiogenesis and extracellular matrix overproduction. In other words, stromal cells change dramatically in number and cell type during the development of obesity. In this regard, excessive energy intake should affect adipose tissue function. Moreover, there is considerable evidence suggesting that the interaction between mature adipocytes and stromal cells in adipose tissue plays a critical role in the regulation of adipocytokine production and lipid storage. Among a number of stromal cells, the role of macrophages has been
most intensively studied.

Obesity and adipose tissue macrophages

In 2003–2004, there were ground-breaking reports demonstrating that macrophages infiltrate adipose tissue in obese mice and humans to form unique histological structures termed crown-like structures (CLS), thereby inducing inflammatory pathways\(^{18-20}\). Evidence has also pointed to the heterogeneity of adipose tissue macrophages in obesity: M1 or “classically activated” (proinflammatory) macrophages and M2 or “alternatively activated” (anti-inflammatory) macrophages\(^{21,22}\). M1 macrophages form CLS, where macrophages surround dead or dying adipocytes and scavenge the residual lipid droplets of dead adipocytes\(^{23-25}\). We and other researchers have shown that monocyte chemoattractant protein-1 (MCP-1) plays a major role in the recruitment of M1 macrophages from the bone marrow\(^{26-28}\). Since M1 macrophages produce proinflammatory cytokines such as tumor necrosis factor-α (TNFα), CLS are a hallmark of adipose tissue inflammation, whose number is positively correlated with systemic insulin resistance\(^{29,30}\). In contrast, M2 macrophages are scattered in interstitial spaces between adipocytes\(^{21,22}\). Besides the increased number of macrophages, the M1 to M2 ratio markedly increases in adipose tissue during the development of obesity\(^{21,22,31-33}\). It is known that proinflammatory mediators such as lipopolysaccharide (LPS) and Th1 cytokine interferon-γ (IFN-γ) promote M1 macrophage polarization\(^{21,22}\). In this regard, we and others have shown that Toll-like receptor 4 (TLR4) is critical for M1 macrophage polarization in obese adipose tissue\(^{34-37}\). TLR4-deficiency protects against obesity-induced adipose tissue inflammation without affecting body weight gain. On the other hand, M2 macrophages are polarized by stimulation with Th2 cytokines such as interleukin-4 (IL-4) and peroxisome proliferator-activated receptors (PPARδ and PPARγ)\(^{31,33,38}\). Deficiency of PPARδ or PPARγ, specifically in macrophages, exacerbates obesity-induced adipose tissue inflammation and glucose intolerance.

Molecular basis of adipose tissue inflammation

It is important to understand how macrophages affect adipose tissue function in obesity. As addressed above, macrophages are major sources of proinflammatory adipocytokines such as TNFα. In addition, we have provided evidence suggesting that a paracrine loop involving saturated fatty acids and TNFα derived from adipocytes and macrophages, respectively, establishes a vicious cycle that augments chronic inflammatory changes\(^{39}\). Indeed, infiltrated macrophages produce TNFα, which acts on the TNF receptor in hypertrophied adipocytes, thereby inducing proinflammatory cytokine production and lipolysis. Among the high concentrations of free fatty acids in adipose tissue, saturated fatty acids may activate TLR4 to induce inflammatory responses in macrophages\(^{40,41}\). Thus, intimate crosstalk between adipocytes and macrophages maintains chronic inflammation of adipose tissue. It is known that ω-3 polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA), potently antagonize the effects of saturated fatty acids. We have shown that dietary supplementation of EPA attenuates obesity-induced adipose tissue inflammation\(^{32}\). Importantly, EPA effectively reverses the macrophage phenotypic switch from M2 to M1, without affecting the macrophage population in adipose tissue. It is interesting to know how dietary lipids influence adipose tissue inflammation.

Obesity-induced adipose tissue fibrosis

In general, chronic inflammatory diseases eventually lead to interstitial fibrosis. In this regard, adipose tissue is not exceptional and obesity-induced adipose tissue inflammation triggers dynamic histological changes including interstitial fibrosis. Interestingly, adipose tissue fibrosis may limit the expandability of adipose tissue during the development of obesity\(^{19}\). For instance, Divoux et al. reported that adipose tissue fibrosis is negatively correlated with adipocyte diameters in human adipose tissue\(^{43}\). Recently, we provided evidence suggesting that macrophage-inducible C-type lectin (Mincle) is a novel regulator of adipose tissue fibrosis\(^{44}\). Mincle is localized to macrophages in CLS, in which macrophages surround dead or dying adipocytes. It is consistent with a previous report showing that Mincle is a sensor for cell death\(^{45}\). When activated by currently unknown endogenous ligands probably released from the adipocytes, Mincle can induce myofibroblast formation and interstitial fibrosis. Indeed, Mincle-deficient mice are protected against obesity-induced adipose tissue fibrosis along with ectopic lipid accumulation in the liver. In addition, Khan et al. reported that mice lacking collagen VI, which is expressed abundantly in adipose tissue, exhibit uninhibited adipose tissue expansion and substantial improvement in insulin sensitivity on a high-fat diet\(^{46}\). It is known that, in response to nutritional conditions, the lipid storage function of adipose tissue is tightly regulated by hormones such as insulin and the sympathetic nervous system\(^{17}\). Chronic inflammation-induced adipose tissue fibrosis may be a novel mechanism of systemic energy homeostasis.
adipocytokines such as TNFα, and a decrease in anti-inflammatory ones such as adiponectin, which is capable of inducing systemic insulin resistance and exacerbating atherosclerotic lesions. Therefore, adipose tissue inflammation may be a therapeutic target to ameliorate dysregulation of a number of adipocytokines. Another possible mediator may be free fatty acids. Adipose tissue inflammation increases insulin resistance in adipocytes, induces lipolysis and limits adipose tissue expandability, all of which contributes to increased serum free fatty acid levels. Among a variety of fatty acids, saturated fatty acids possess proinflammatory properties through various pathways including TLRs, oxidative stress and endoplasmic stress. Moreover, increased serum free fatty acids induce ectopic lipid accumulation and tissue dysfunction. In contrast, chronic inflammation inhibits the synthesis and release of palmitoleic acid in adipose tissue. Palmi- toleic acid potently improves insulin sensitivity in liver and skeletal muscle. Accordingly, it is likely that adipose tissue inflammation controls the quality, as well as quantity, of serum free fatty acids (FFAs), thereby regulating systemic metabolic homeostasis.

Leptin and B cell development in malnutrition

It is known that nutritional deprivation or malnutrition suppresses immune function in humans and animals, thereby conferring higher susceptibility to infectious diseases. For instance, nutritional deprivation induces atrophy of lymphoid tissues such as thymus and spleen and decreases the number of circulating T and B cells. In this regard, leptin may be one of the key molecules linking nutritional status with immune function. Leptin is exclusively produced in adipose tissue in response to the nutritional status and acts directly on the hypothalamus, thereby regulating food intake and energy expenditure. Recently, we reported that leptin administration effectively restores alteration of B cell development in the bone marrow of fasted mice. Since leptin-deficient ob/ob mice show similar B cell alteration as fasted mice, leptin rather than nutritional status, is considered critical in B cell development in the bone marrow. Interestingly, central leptin administration is sufficient to eliminate the effect of food deprivation, although leptin receptors are expressed in a variety of peripheral tissues including immune cells. As a molecular mechanism, corticosterone is involved in the central leptin signaling-mediated regulation of B cell development in the bone marrow. Thus, these findings highlight that leptin signaling in the central nervous system, which is inherent to integrate nutritional information from throughout the organism, is capable of controlling immune function.

Concluding remarks

During the past decade, there has been remarkable progress in understanding the molecular mechanism of obesity-induced adipose tissue inflammation. Now, it is well-known that a variety of stromal cells induce adipose tissue remodeling, which impairs adipose tissue function such as lipid storage and adipocytokine production, and leads to systemic metabolic derangements. In this regard, adipose tissue senses systemic nutritional conditions and regulates inflammatory responses. In contrast, nutritional deprivation or malnutrition results in immune dysfunction, at least partly, through a leptin-mediated mechanism. It is important to further investigate the interaction of nutrition and immunity, which would help improve understanding of the molecular mechanism of life style-related diseases.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

References


