REVIEW

Adipocyte Death and Chronic Inflammation in Obesity

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Abstract : Cell death is closely linked to many diseases including cancer, neurodegenerative diseases, autoimmune diseases, and metabolic disorders. Increased adipocyte death has been reported during the development of obesity. Adipocyte death may be caused by excessive stress during obesity-related adipose tissue remodeling. Adipose tissue macrophages are key players in obesity-related inflammation and systemic insulin resistance. Accumulating evidence suggests that adipocyte death is involved in immune cell function and initiates inflammation through an interaction with macrophages ; however, the precise mechanisms remain largely unknown. This review focuses on the contribution of dead cells (particularly dead adipocytes in adipose tissue) to the pathophysiological conditions associated with obesity. J. Med. Invest. 64 : 193-196, August, 2017

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INTRODUCTION

The balance between cell death and survival is one of the most important factors for optimal tissue development and homeostasis in living organisms. Dysfunctional cells are removed by programmed cell death, thereby maintaining normal tissue functions. Severe damage and viral infections also trigger programmed cell death. However, when cells are exposed to intense stress, heat, radiation, and chemicals, another type of cell death occurs. Accidental cell death, necrosis, is morphologically identified by the swelling of organelles, an increased cell volume, and disruption of the cell membrane and is considered to be a cause of inflammation and related diseases (1).

Most programmed cell death is attributed to apoptosis, which is characterized by a condensed cytosol, marginalized chromatin, and nuclear fragmentation. During the process of apoptosis, dying cells break into apoptotic bodies that are rapidly phagocytosed ; therefore, this type of cell death is not considered to be a cause of inflammation (2). However, previous studies revealed that programmed cell death also affects immunity and induces inflammation, and, in recent years, inappropriate cell death was shown to be involved in metabolic diseases. This review focuses on the contribution of dead cells (particularly dead adipocytes in adipose tissue) to the pathophysiological conditions associated with obesity.

CELL DEATH AND OBESITY-RELATED COMPLICATIONS

Low-grade chronic inflammation in adipose tissue has been attracting increasing attention as an onset mechanism for obesity-related complications. “Chronic inflammation” is considered to be associated with autoimmune diseases such as rheumatoid arthritis, and allergy diseases including pneumonia and atopic dermatitis ; however, recent findings suggest that it plays a more prominent role in a number of diseases including cancer, atherosclerosis, and Alzheimer’s disease. Chronic inflammation also has a pivotal role in obesity-related complications including metabolic syndrome, insulin resistance, type 2 diabetes, and non-alcoholic steatohepatitis (NASH). Immune cells such as macrophages were previously reported to be responsible for cytokine production and the establishment of chronic inflammation within adipose tissue in obese individuals (3).

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ROLE OF MACROPHAGES IN INFLAMMATION

Since leptin was discovered as an adipokine secreted from adipose tissue (4), many other adipokines have been reported. Adipose tissue is now regarded as the largest endocrine organ that contributes to whole body metabolism through adipokine secretion. Other than adipocytes, immune cells such as macrophages have recently been discovered in adipose tissue (5). Subsequent studies demonstrated the significant role of adipose tissue macrophages in metabolic disorder associated with obesity (3).

The infiltration of macrophages into adipose tissue is enhanced with obesity. Elevated levels of macrophage markers have been observed in adipose tissue from obese mouse models (DIO, ob/ob, and db/db) (6). Furthermore, adipose tissue macrophages have been shown to induce insulin resistance by triggering inflammation. Bone marrow transplantation from TNF-alpha-deficient mice improved obesity-related insulin resistance more than wild-type bone marrow (7).

ADIPOCYTE DEATH AND MACROPHAGE INFILTRATION

The next question is “how macrophages are recruited to adipose tissue in the obese state?”. Many factors have been suggested as possible initiators of recruitment including fatty acid flux (8), abnormal adipokine secretion, and cell-free DNA from adipocytes (9). In recent years, enhanced adipocyte death has been attracting increasing attention. The majority of adipose tissue macrophages localize to dead adipocytes and form a crown-like structure (CLS)

(10). CLS has rarely been detected in lean mice, whereas the number of CLS formed increased by 30-fold in obese mice (10). Ariel *et al.* examined the effects of adipocyte death on metabolic disorder associated with obesity using Bid knockout mice (11). They showed that the deletion of Bid, a key pro-apoptotic molecule, did not affect weight gain, but protected mice against chronic inflammation and insulin resistance. The infiltration of macrophages into adipose tissue was also decreased by the inhibition of adipocyte death. Based on these findings, adipocyte death associated with obesity may be a novel factor recruiting macrophages into adipose tissue.

CAUSE OF ADIPOCYTE DEATH

What causes adipocyte death in obesity? Adipocyte death may be closely related to adipose tissue remodeling (12). Similar to other tissues, cellular turnover occurs in adipose tissue throughout life (13). New adipocytes have been suggested to differentiate from precursor cells within adipose tissue (14), whereas old adipocytes undergo apoptosis and are removed by macrophages. The removal of aged adipocytes and replacement of newly differentiated cells are stimulated during the development of obesity (13). Limited information is available on the cellular and molecular mechanisms regulating the replication and apoptosis of fat cells during adipose tissue expansion. New findings showed that a high-fat diet in mice rapidly and transiently induced the proliferation of adipocyte precursors in visceral adipose tissue and this process required Akt2 signaling (15). During the process of adipose tissue expansion, the microenvironment within the tissue markedly changes, which includes increased mechanical (16) and oxidative stress (17) as well as hypoxic conditions (18). This altered microenvironment is considered to induce cell death associated with obesity.

In addition to the adipose tissue microenvironment, another mechanism has been proposed as the cause of cell death. A correlation was previously reported between adipocyte cell size and the frequency of fat cell apoptosis or metabolic disorder, indicating that an increase in adipocyte cell size, hypertrophy, initiates cell death. Important findings were obtained from a study with hormone-sensitive lipase (HSL), a major lipase in adipocytes, knockout mice. Due to the disruption of the lipolysis process, HSL knockout mice showed an increased adipocyte cell size without obesity (19). Increased macrophage infiltration and inflammation in adipose tissue were also observed in the knockout mouse (10). These findings imply that hypertrophy itself is essential for adipocyte apoptosis.

ADIPOCYTE DEATH MACROPHAGE ACTIVATION

Macrophages in CLS are positive for pro-inflammatory cytokines such as TNF-alpha and IL-6 ; therefore, CLS is recognized as a center of inflammatory responses in obesity (10).

One of the major mechanisms linking cell death and inflammation is the DAMP-mediated activation of the immune system. DAMPs are molecules that include nuclear and cytosolic proteins. Following necrosis (or necrosis secondary to apoptosis), DAMPs are released from dying cells and stimulate immune cells. For example, HMGB1 (High Mobility Group Box 1), a DAMP, induces the expression of pro-inflammatory cytokines and adhesion factors in immune cells through the receptor for advanced glycation endproducts (RAGE) (20). In addition, direct crosstalk between macrophages and dead cells has been proposed.

The co-culturing of macrophages with apoptotic cells was found to induce marked increases in pro-inflammatory cytokines such as IL-1b, IL-6, and MIP-2 (21). Inflammatory responses induced by apoptotic cells were canceled by the inhibition of phosphatidylserine and vitronectin receptors (22), implying that the direct interaction of macrophages with dead cells triggered inflammatory activation. The molecular basis of phagocytosis-mediated responses has not yet been elucidated. Phagocytes have multiple receptors on cell membranes in order to identify molecules on the surfaces of apoptotic cells and initiate engulfment. These receptors include scavenger receptors, integrins, and CD91 (23). Furthermore, phagocytes have another type of receptor that recognizes pathogens and specific ligands on apoptotic cells, and induces inflammatory reactions such as FcR and the TLR family.

FcR, expressed on phagocytes, may contribute to the clearance of dead cells (24) and inflammatory reactions after phagocytosis. Previous studies reported that the cross-linking of FcR with particles triggered pro-inflammatory cytokine generation in monocytes (25) and macrophages (26). FcR-cross linking has been shown to activate mitogen-activated protein kinase (MAPK) family members including p42MAPK, p38, and c-Jun NH2-terminal kinase (JNK)/stress-activated protein kinases (26). The inhibition of p42MAPK by PD098059 decreased FcR-mediated TNF-alpha production. TLRs have also been proposed to define the consequences of phagocytosis (27).

However, several studies have shown that the phagocytosis of apoptotic cells does not induce inflammation. Macrophages derived from humans phagocytosed aged neutrophils and without inflammatory responses (28), whereas other *in vitro* studies reported contrasting findings. The discrepancy in these *in vitro* studies may be explained by differences in culture conditions ; however, the precise reasons remain unknown.

In the context of obesity and its complications, information on crosstalk between dead adipocytes and macrophages has been accumulating. Complements are known to enhance phagocytosis by linking apoptotic cells and phagocytes, and contribute to the rapid clearance of dead cells. Nagy examined the role of C1q, one of the complement molecules, in obesity (29). The knockout of C1q had no effect on body weight, but improved glucose tolerance and chronic inflammation. Moreover, obesity-related adipocyte death was slightly increased in knockout mice, implying that a reduction in the efficacy of clearing dead adipocytes may reduce macrophage inflammatory activation.

Dysregulated cell death could induce inflammation and trigger a variety of diseases including obesity related complications. On the other hand, properly controlled cell deaths are definitely necessary for optimal tissue development and repair. To understand precise role of cell death and its involvement on diseases, we need to know more about when, how and what types of cell death occur. To answer these questions, live imaging probes for cell death detection which utilize caspase activity have been developed. Those probes enable us to monitor spatial and temporal activations of caspase at single cell level.

For example, Takemoto *et al.* have developed SCAT3 technology to sense caspase 3 activity (30). Live imaging in transgenic mouse model expressing SCAT3 revealed well-coordinated apoptosis cell death during the process of neural tube closure (31).

CONCLUSION

The infiltration and activation of adipose tissue macrophages are hallmarks of obesity, which induces local inflammation and whole body insulin resistance. Based on accumulating findings, adipocyte death appears to contribute to this process (Fig. 1). The elucidation of the roles of dead adipocytes in the pathology of obesity represents a demanding challenge in future studies.

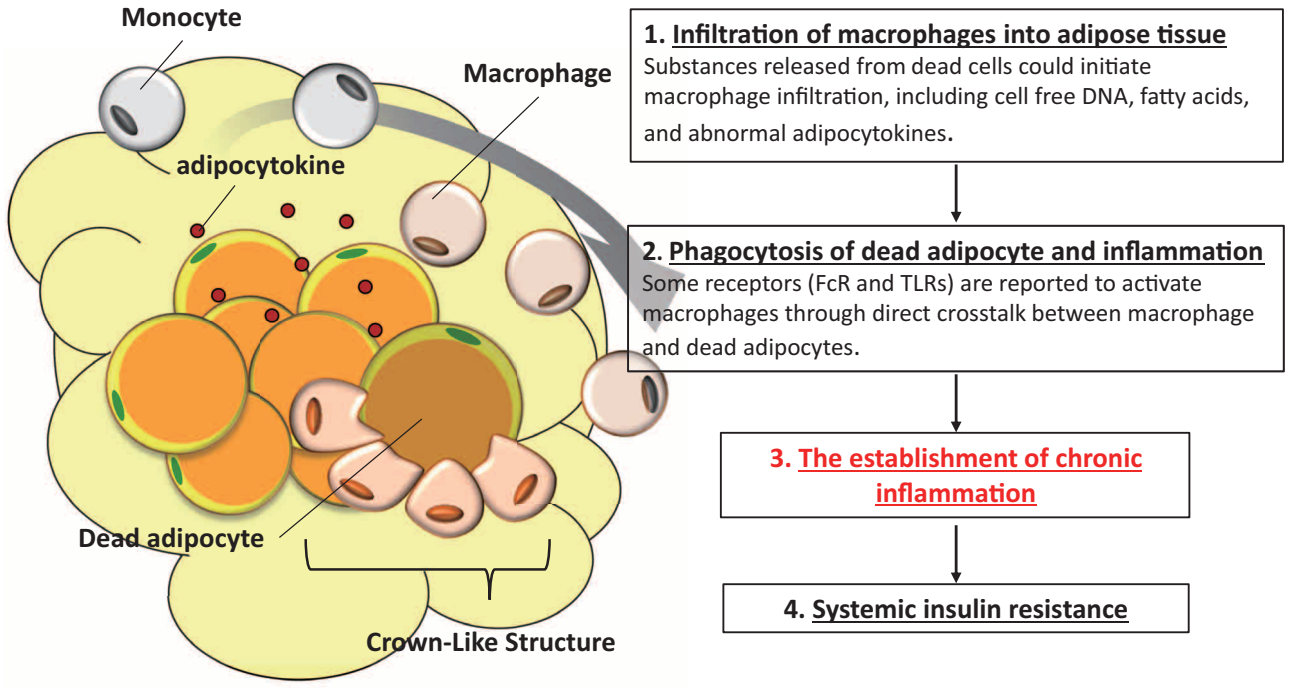

Fig1. The involvement of adipocyte death in local inflammation in obesity.

COI

No potential COI to disclose.

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