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ADIPOSE TISSUE HYPOXIA IN OBESITY

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Abstract ▶ Obesity is linked to a variety of metabolic disorders, such as insulin resistance and atherosclerosis. The increased incidence of obesity has led to rise in interest in the biology of white adipose tissue (WAT). The tissue is no longer considered as a passive fat storage tissue but is a key endocrine and signaling organ secreting a multiplicity of protein factors called adipokines. In obesity, there is an enhanced secretion of a number of adipokines underpinning the role of inflammation in white adipose tissue towards the development of obesity and associated diseases. There is a substantial evidence, particularly from animal studies, that hypoxia develops in adipose tissue as the tissue mass expands in obesity, and the reduction in PO2 is considered to underlie the inflammatory response. The cells present within the WAT respond to hypoxia, by inhibiting the differentiation of pre-adipocytes to adipocytes and instead being transformed into leptin-secreting cells. The dynamic change found in the adipose tissue can be referred to as "adipose tissue remodeling," in which stromal cells change dramatically in number and type during the course of obesity. Among stromal cells, infiltration of macrophages in the adipose tissue precedes the development of insulin resistance in animal models, suggesting that they are responsible for obesity-related adipose tissue inflammation. Understanding the molecular mechanism underlying adipose tissue remodeling may lead to the identification of novel, therapeutic strategies to prevent obesity-induced adipose tissue inflammation.

Key Words: Adipose tissue, Obesity, Hypoxia, Macrophage infiltration.

Introduction

Obesity

Obesity is a medical condition in which excess body fat accumulates to the extent that it may have a negative effect on health. A crude measure of obesity is the body mass index (BMI), measured by a person's weight (in kilograms) divided by the square of height (in meters). A person with a BMI of > 25 is termed as "obese". Obesity increases the likelihood of various diseases, particularly heart disease, type2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis.[1] Obesity is attributed to hypertrophy and hyperplasia of adipocytes. Adipocytes become hypertrophic during the development of obesity, and their size increases up to 140–180μm in diameter[2] which is beyond the diffusion limit of oxygen. Therefore, hypertrophic adipocytes might endure less than adequate oxygen supply and turn hypoxic.[3]

Hypoxia and its impact on adipose tissue

Hypoxia is defined as a diminished availability of oxygen to body tissues. The consequences of, and adaptations to, low O_2 tension have been extensively investigated.[4,5] Molecular oxygen (O_2) is essential for maintaining normal tissue functions ranging from cellular energy production to regulation of a multitude of intracellular signal transduction pathways. Hypoxia is one of the central mechanisms postulated to explain the development of inflammation and the subsequent metabolic dysfunction of WAT in obesity.[6] There is a growing recognition that O_2 levels are far from being constant in all tissues. For example, while the general level of tissue oxygenation (pO2) is 45–50 mm Hg, that of the thymus is 10mm Hg, for the brain it is as low as 0.4–8 mm Hg and the center of solid tumors can essentially be anorexic. In the case of WAT, it was proposed that as fat mass expands in the obese, large adipocytes become distant from the vasculature and areas of O_2 deprivation occur.[7]

Hypoxia was subsequently demonstrated in WAT of genetically obese rodents (obese ob/ob and KKAy mice) as well as in mice with diet induced obesity. Two distinct experimental approaches documented hypoxia in these obese mice. One study utilized the hypoxia marker pimonidazole that showed low pO_2 qualitatively. Quantitative measurements have been obtained using needle type O_2 sensors, and these found between 2 and 3.5 fold reductions in pO_2 in WAT of ob/ob and dietary obese mice relative to lean controls.[8]

Effect of Hypoxia on the stromal vascular cells, macrophages and pre-adipocytes

Hypoxia has been shown to increase the secretion of key cytokines as well as of VEGF from the cells of the stromal-vascular fraction (SV) of human adipose tissue. The cytokines include TNF-β, IL-6, IL-10, and CCL-2 (MCP-1). The SV fraction is composed of different types of cell and effectively all the cells within adipose tissue rae involved in the release of cytokines and adipokines. It is therefore difficult to attribute the hypoxic response in the SV fraction as a whole to a specific cell type. However, the effects were reported to be enhanced in SV fractions enriched in the macrophage marker. This implies that macrophages are the major source of inflammatory cytokines within the SV under hypoxic conditions.[9]

Direct studies on macrophages, or macrophage cell lines, indicate that they respond strongly to hypoxia with a stimulation of the production of a range of cytokines and other inflammation-related factors.[10] In a recent study, hypoxia has been reported to up-regulate TLR-4 (Toll-like receptor 4) expression via HIF-1 in RAW264.7 cells. Interrogation of microarray datasets does not suggest, however, any such hypoxia-induced up-regulation of TLR-4 expression in adipocytes.[11] Pre-adipocytes, as the precursors of adipocytes, are key cells within adipose tissue, and their response to hypoxic conditions has been explored. A major effect of low O_2 tension on pre-adipocytes is to inhibit their differentiation to adipocytes. Expression of the PPARβ nuclear transcription factor is down regulated in pre-adipocytes by hypoxia, through Hypoxia Induced Factor (HIF)-1 alpha.[12]

PPARβ expression is also inhibited by hypoxia in mature adipocytes and this may explain, at least in part, the hypoxia-induced changes in the expression of genes such as adiponectin. These effects may in turn upregulate C/EBP homologous protein (CHOP) in adipose tissue of obese animals and in 3T3-L1 adipocytes exposed to hypoxia. The down-regulation of PPARβ and inhibition of adipocyte differentiation in a low O_2 environment may inhibit fat cell recruitment in obesity. This would be consistent with the concept that fat cell number stays constant in adult obese (and normal weight) subjects as the number of adipocytes is set in childhood and adolescence.[13]

Other than being the precursors of mature adipocytes, pre-adipocytes also act as inflammatory cells expressing and releasing a range of inflammation related factors, particularly in response to stimulation by macrophage-derived mediators. Hypoxia leads to the stabilization of HIF-1β, leading to its accumulation. This in turn modulates the expression of several genes that are hypoxia-sensitive in adipocytes, including VEGF, FABP4 (aP2), and GLUT1, PAI-1, IL-4, and IL-6.[14]

One of the most intriguing aspects of the response of pre-adipocytes to hypoxia relates to leptin expression. Pre-adipocytes are considered not to express the LEP gene. Its expression generally occurs around 3–4 days after the induction of differentiation. Hence, the expression of leptin is a marker of adipocyte differentiation. In several cell types, including trophoblast-derived BeWo cells and breast cancer cell lines, which normally show very little or no leptin expression, exposure to hypoxia leads to the induction of leptin synthesis. Similarly, incubation of human pre-adipocytes in low PO_2 results in the marked induction of leptin gene expression.[15] Thus hypoxia turns pre-adipocytes into leptin-secreting endocrine cells. Pre-adipocyte-derived leptin may play

a specific local autocrine/paracrine role within adipose tissue.

Obesity induced macrophage infiltration in adipose tissue

Among stromal cells, macrophages play the key role in adipose tissue remodeling. Adipose tissue remodeling may be viewed as a result of chronic inflammation that includes adipocyte hypertrophy, macrophage infiltration, and adipocyte-macrophage interaction. There is a considerable evidence for the pathophysiologic role of the MCP-1/CCR2 pathway in macrophage infiltration into obese adipose tissue. Weisberg et al. reported the attenuation of macrophage accumulation and chronic inflammation in the adipose tissue from CCR2 ($CCR2^{-/-}$ mice) fed with high-fat diet. Moreover, two previous studies with transgenic mice overexpressing MCP-1 in the adipose tissue and MCP-1-deficient mice ($MCP\text{-}1^{-/-}$ mice) showed that MCP-1 plays a role in the recruitment of macrophages into obese adipose tissue.[16] Through a combination of a real-time horizontal chemotaxis assay *in vitro* and bone marrow transplantation techniques *in vivo*, it has been demonstrated that enhanced CCR2 expression in bone marrow cells is involved in macrophage infiltration into obese adipose tissue.[17] In addition to the MCP-1/CCR2 pathway, there are several reports suggesting the potential involvement of other chemotactic factors like osteopontin, angiopoietin-like protein-2, and CXCL14 in obesity-induced macrophage infiltration. Importantly, inhibition of macrophage infiltration into obese adipose tissue through genetic and/or pharmacologic strategies improved the dysregulation of adipocytokine production, thereby leading to the amelioration of obesity-induced adipose tissue inflammation and insulin resistance.[17] Understanding the molecular mechanisms underlying increased macrophage infiltration into obese adipose tissue may lead to the identification of novel therapeutic strategies to prevent or treat obesity-induced adipose tissue inflammation.

Conclusion

Obesity may be viewed as a chronic, low-grade inflammatory and metabolic disease. Chronic inflammation within the adipose tissue results in the dysregulation of adipocytokine production, thereby contributing to the pathophysiology of the metabolic syndrome. Among stromal cells, macrophages play a critical role in obesity-related adipose tissue inflammation. The hypoxia in adipose tissue plays the pivotal role in adipose tissue remodeling in obesity. The adipose tissue is capable of affecting multiple tissues and organs by virtue of a large number of adipocytokines and thus, influences a variety of physiologic and pathophysiologic processes. Reversing hypoxia, or attenuating the O_2-signaling pathways, whether through the HIFs or other regulatory factors, presents novel therapeutic strategies.

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