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Relationship between NK cells and insulin resistance in adipose tissue

Abstract

Visceral obesity is closely related to insulin resistance, but the exact mechanism is not clear. In recent years, the role of immune inflammation in metabolic diseases has attracted more and more attention in the academic field. Recent studies have confirmed that some cytokines and inflammatory mediators secreted by the immune cells in dipose tissue involved in insulin resistance. NK cells act as an important regulator and play an important role in obesity induced macrophage polarization and insulin resistance in the visceral adipose tissue. This review will explain the relationship between NK cells and insulin resistance in visceral adipose tissue and the mechanism of insulin resistance.

Keywords: adipose tissue, NK cells, insulin resistance

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Mini review

As a consequence of sustained over nutrition, obesity has become epidemic in many countries worldwide. The prevalence rates are continuing to increase, most rapidly in developing countries. Obesity predisposes individuals to an increased risk of developing several diseases, including atherosclerosis, diabetes, non-alcoholic fatty liver disease and some certain cancers. Obesity, in particular visceral obesity, which is accumulation of adipose tissue inside the abdominal cavity, is associated with resistance to the effects of insulin [IR (insulin resistance)], often leading to the development of T2DM (Type 2 diabetes mellitus). In addition to these associations between obesity and disease, research in the past few years has identified important pathways that link metabolism with the immune system and vice versa. Many of these interactions between the metabolic and immune systems seem to be orchestrated by a complex network of soluble mediators derived from immune cells and adipocytes.[1,2] Obesity induced inflammation is the basis for the development of insulin resistance and type 2 diabetes. The most common underlying cause is central obesity, although insulin resistance is also possible in normal-weight individuals. Excess abdominal adipose tissue has been shown to release increased amounts of free fatty acids, tumor necrosis factor α (TNFα), adiponectin, leptin, IL-6 and some other adipokines, which affect insulin signalling.[3] The inflammatory response is mediated by immune cells in adipose tissue, macrophages infiltrate adipose tissue during obesity and contribute to insulin resistance.[4] In recent years it has been discovered that tissue-resident NK cells are key regulators of macrophage polarization and insulin resistance in response to obesity-induced adipocyte stress.[5] Visceral adipose tissue is more closely associated with insulin resistance than subcutaneous adipose tissue, according to the report.[6] NK cells, acting as an important immune cell, may be a cause of the different relationship between the two depot adipose tissue (visceral adipose tissue, VAT and subcutaneous adipose tissue, SAT) and insulin resistance.

NK cells

NK cells, namely natural killer cells, are a group of heterogeneous multi-functional immune cells. It is a kind of killer cells with natural cytotoxic activity, different from T, B lymphocytes and cytotoxic T cells. NK cells are widely distributed in the blood, liver, spleen, lung and other organs, but also in the thymus, lymph nodes and bone marrow. In obese subjects, adipose tissue NK cells (ATNK) are comprised of a greater percent of CD56bright cells, compared to peripheral blood NK cells (PBNK). ATNK in obese subjects express higher levels of activation markers, including CD158, NKG2D, NKp46, and CD27. CD56bright NK cells within adipose tissue are prone to secrete cytokines promoting adipose tissue inflammation.[7,8]

Sources of NK cells in visceral adipose tissue

A number of different cell types contribute to the cellular architecture of adipose tissue. Although the adipocyte is functionally making important contributions to systemic metabolic homeostatis, several additional cell types contribute a supportive role to bestow maximal flexibility on the tissue with respect to many biosynthetic and catabolic processes, depending on the metabolic state. These cells include vascular endothelial cells, a host of immune cells, adipocyte precursor cells and fibroblasts. These cell types give rise to a tissue with remarkable flexibility with respect to expansion and contraction, while optimizing the ability of the tissue to act as an endocrine organ through the release of many protein factors, critically influencing systemic lipid homeostasis and biochemically contributing many metabolites.[9] Obesity drives immune cells to accumulate in visceral adipose tissue. Compared with that of neutrophils, the increase in the numbers of adipose tissue NK cells appears to be delayed, occurring in weeks, rather than days after the start of HFD feeding.[10] Animal experiments show that fat in obese subjects generated a local environment that supported greater numbers of NK cells. The obesity-induced increase in the number of NK cells in the VAT is probably primarily due to local proliferation.[5]

Relationship between NK cells and insulin resistance in visceral adipose tissue

Insulin resistance (IR) is a state of attenuated response of target tissues to insulin, resulting in its inability to provide normal glucose and lipid homeostasis. It arises from central Obesity.[11] Insulin resistance is a common cause of metabolic syndrome and type 2 diabetes

mellitus. Insulin resistance in the adipose tissue affects systemic lipid and glucose homeostasis.12 The intracellular cytokine production and cell surface marker expression of NK cells were influenced by heterogeneous cocktail of human adipokines. Adipokine may induce release of autoimmune inflammatory mediators to activate NK cells which contributing to chronic low-grade inflammatory state13 and this inflammation causes insulin resistance. A study on transgenic mouse model indicates that NK cell ablation was associated with decreased total macrophage infiltration in intra-abdominal adipose tissue, but macrophage infiltration in subcutaneous adipose tissue and spleen was unaffected. NK cell ablation was associated with modest improvement in insulin sensitivity but had no effect on tissue transcript levels of inflammatory cytokines. Thus NK cells play a role in promoting intra-abdominal adipose tissue macrophage infiltration and systemic insulin resistance in obesity.14

Pathogenesis of insulin resistance induced by NK cells

There is increasing evidence showing that inflammation of VAT is an important pathogenic mediator of the development of obesity-induced insulin resistance. It is now generally accepted that tissue-resident immune cells play a major role in the regulation of obesity-induced inflammation. All published studies strongly show that obesity increases the numbers of total and CD11c+ adipose tissue macrophages (ATMs) and that the infiltrating ATMs express high levels of pro-inflammatory cytokines such as TNFα, and then contribuce to inflammation and insulin resistance in adipose tissue. These supports the notion that ATMs regulate the development of systemic insulin resistance in obesity.15 Animal experiments show that high-fat diet (HFD) increases NK cell numbers and the production of proinflammatory cytokines, notably TNFa, in epididymal, but not subcutaneous, fat depots. The loss of epididymal NK cells improves obesity-induced insulin resistance, while NK cell expansion exacerbates the condition. NK cells and ATMs together create a self-amplifying proinflammatory adipose tissue milieu that promotes insulin resistance. Thus, epididymal NK cells are more likely to alter ATM functions and metabolic homeostasis by secreting inflammatory modulators.16

Obesity drove the upregulation of ligands of the NK cell-activating receptor NCR1 on adipocytes; this stimulated NK cell proliferation and interferon-γ (IFN-γ) production, which in turn triggered the differentiation of proinflammatory macrophages and promoted insulin resistance. Deficiency of NK cells, NCR1 or IFN-γ prevented the accumulation of proinflammatory macrophages in VAT and greatly ameliorated insulin sensitivity. Thus NK cells are key regulators of macrophage polarization and insulin resistance in response to obesity-induced adipocyte stress.5

The different relationship between VAT, SAT and insulin resistance may be related to NK cells

Adipose tissue distributed in the abdominal visceral carry a much greater risk for metabolic disorders than does adipose tissue distributed subcutaneously. The health risks associated with obesity vary depending on the location of adipose tissue. Rather, different adipose depots have different properties that can make important consequences on health.17 VAT is associated with insulin resistance, diabetes mellitus, dyslipidaemia, hypertension, atherosclerosis, hepatic steatosis, and overall mortality, whereas SAT have intrinsic beneficial metabolic properties.18 VAT is characterized by an inflammatory response in the presence of obesity, which is mediated by a large number of inflammatory cytokines, and is currently believed

to be associated with a large increase in the number of immune cells in the VAT.19 NK cells, acting as an important immune cell, may be a cause of the different relationship between the two depot adipose tissue (VAT and SAT) and insulin resistance.

Conclusion

Although dietary and lifestyle modifications can be effective for the treatment of obesity and prevention of diabetes, these lifestyle changes are difficult to maintain and regain of weight is typical. The primary cause of T2DM is obesity-driven insulin resistance.20 So the mechanism of insulin resistance is helpful to understand the pathogenesis, early diagnosis and new therapeutic target of diabetes. The relationship of NK cells in adipose tissue and insulin resistance provides a new perspective of diabetic pathogenesis. The NK cell-macrophage axis in adipose tissue therefore is a promising new target for the treatment of patients with metabolic syndrome to reduce the risk of progression to type 2 diabetes mellitus.

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Conflict of interest

Author declares that there is no conflict of interest.

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