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Features of Immunological Changes in Metabolic Syndrome

B.Z. Khamdamov[1], O.T. Sattarov[2], A.Z. Isomutdinov[3]

ABSTRACT

For several decades, it has been believed that an increased inflammatory background has a great impact on glucose metabolism. For example, the expansion and infiltration of pro-inflammatory immune cells is present in several metabolic active tissues during the development of type 2 diabetes. This pro-inflammatory environment has huge implications for organ function, as seen in the development of insulin resistance, beta-cell dysfunction, and nonalcoholic steatohepatitis. The trigger or origin of this inflammatory response is still elusive. There is great opportunity to identify and describe the underlying metabolic and inflammatory pathways, however, the resulting research is often contradictory. In particular, models in experimental mice often produce inconclusive results, and numerous inflammatory messengers have a dual role. In addition, the active components of the immune system perform important physiological functions (other than pure inflammation) and have tissue responses. These results highlight that the immune system is a complex organization that is often neither pro- nor anti-inflammatory per se. In addition, a controlled (acute) inflammatory response is important for the host to control invading pathogens and remove damaged tissues.

Keywords: metabolic syndrome, type 2 diabetes mellitus, obesity, immunological changes

Patients with obesity and type 2 diabetes mellitus are characterized by the presence of the so-called "metabolic inflammation", which is associated with disorders of metabolic processes of glucose metabolism.

For example, studies by J. Spranger [1] and C. Liu [2] revealed an increase in the level of cytokines in the blood of patients with type 2 diabetes mellitus. At the same time, a group of researchers led by R. Marfella [3] revealed an increase in the level of cytokines in the blood in women with metabolic syndrome and its negative effect on menopause.

In 2019, W. Zhou et al. [4] in their studies proved a high inflammatory risk of developing a respiratory viral infection among patients with insulin resistance. In the same year, D. Michalovich et al. [5] found a close relationship between the presence of an inflammatory background, a more severe course of bronchial asthma, and changes in the intestinal microbiota.

[1] Bukhara State Medical Institute, Bukhara, Uzbekistan, e-mail: dr.hamdamov@mail.ru

[2] Tashkent Medical Academy, Tashkent, Uzbekistan, e-mail: doctoroybek@rambler.ru

[3] Regional Multidisciplinary Clinic, Bukhara, Uzbekistan, e-mail: azamzokirovic@gmail.com

Pharmacological effects on the gut microbiota had a positive effect on the development of glucose tolerance. Such results were obtained by V. Sabapathy et al. [6] in experimental studies on mice, which made it possible to isolate a new hybrid cytokine IL-233, which is produced by genetically modified Escherichia coli by fusion of mouse IL-2 and mouse IL-33.

Studies in this direction have shown the possibility of a new pharmacological approach to reduce metabolic inflammation in patients with type 2 diabetes mellitus. Such strategies are based on blocked IL-1 receptors, IL-1β antagonism, inhibition of the intracellular pro-inflammatory pathway NF-ϰB, and TNF antagonism.

The results of the correlation analysis by J. Lu et al. [7] confirmed that adipose tissue was one of the first in which inflammation was strongly correlated with insulin resistance. Adipose tissue has been shown to contain a variety of immune cells, including T cells, eosinophils, and mast cells, which keep resident macrophages in a polarized or alternatively activated state.

Studies by C.N. Lumeng et al. [8] and E.G. Hong et al. [9] have shown that the secretion of the anti-inflammatory cytokine IL-10 from macrophages protects lean mice from insulin resistance.

E. Van et al. [10] proved that obese mice and people with type 2 diabetes mellitus have lower expression of IL-10 and higher pro-inflammatory signals. Obese people with metabolic syndrome had lower levels of IL-10 compared to subjects without metabolic syndrome. In addition, overexpression of IL-10 in mouse muscle tissue improved insulin sensitivity even on a high-fat diet. These results suggest a key role for IL-10 in the prevention of inflammation in people with metabolic syndrome.

Other important but less studied anti-inflammatory cytokines include IL-4 and IL-13. IL-4 promotes glucose tolerance and inhibits adipogenesis. In addition, it promotes alternative activation of macrophages. Genetic variations in the IL-4 promoter have been associated with susceptibility to type 2 diabetes. However, there is still little information in the literature to draw definitive conclusions in this direction.

IL-13 has a similar structure to IL-4, has anti-inflammatory properties, and promotes the activation of alternative macrophages. Surprisingly, both cytokines were elevated in the blood of obese people, which was associated with lower physical activity.

Another study confirmed these results by showing elevated levels in insulin-resistant people that were positively correlated with hyperglycemia [11]. A study in mice indicates impaired activity of IL-13 receptors.

Classically activated macrophages are particularly involved in the metabolic inflammation seen in obesity and type 2 diabetes. Macrophages of this species are usually responsible for the secretion of pro-inflammatory cytokines and are associated with the development of type 2 diabetes mellitus by altering tissue functions.

Chemokines are able to attract immune cells to metabolic active tissues [12]. Monocyte chemoattractant protein-1 is a strong chemokine for monocytes, and its expression has been increased in adipose tissue in obese humans and rodents.

In rodents, overexpression of monocyte chemoattractant protein-1 in adipose tissue increased macrophage infiltration and mediated insulin resistance. At the same time, monocyte chemoattractant protein-1 stands out in combination with a high-fat diet, nutrition, increased development of insulin resistance compared to wild-type mice. Although this observation was not observed in another study [13]: higher production of chemokine in adipose tissue with obesity was associated with infiltration of immune cells and the development of insulin resistance.

A recent study suggests that obesity-related insulin resistance precedes the infiltration of pro-inflammatory macrophages, providing insight into the cause-consequence dilemma [14]. First, insulin resistance, which was genetically caused by the knock-out of the mammalian target of the rapamycin-2 complex (mTORC2)), coincides with increased expression of monocyte chemoattractant protein-1, monocyte infiltration, and differentiation into pro-inflammatory macrophages. Second, insulin resistance in wild-type mice preceded macrophage accumulation during diet-induced obesity. Third, adipose tissue from insulin-resistant obese patients had a lower mTORC2 response, high expression of monocyte chemoattractant protein-1, and high macrophage content. Thus, insulin resistance can be a consequence of obesity and the cause of macrophage infiltration, which, in turn, increases the development of diabetes mellitus.

Human pancreatic islets also express and secrete monocyte chemoattractant protein-1. The expression of this protein was increased after exposure to pro-inflammatory stimuli such as lipopolysaccharide. In addition, overexpression of MCP1 in pancreatic beta cells led to reliable infiltration of macrophages in islets and the spontaneous development of diabetes. These results suggest an important role for macrophage cells in the pathogenesis of insulin resistance and beta cell dysfunction through immune cell infiltration.

Infiltration of cytotoxic CD8 T cells into the adipose tissue of obese mice precedes the accumulation of macrophages. In fact, genetic depletion of CD8+ T cells reduced macrophage infiltration, adipose tissue inflam-

mation, and insulin resistance, while receiving CD8+ T cell transmission exacerbated adipose tissue inflammation. In addition, T cells in obese adipose tissue produce more pro-inflammatory mediators compared to lean controls. In addition, the amount of interferon (IFN-γ) producing T-helper (Th1) cells in visceral adipose tissue of a person is positively correlated with a systemic inflammatory background, but is not associated with insulin resistance; however, anti-inflammatory Th2 cells are negatively correlated with insulin resistance. In addition, obese mice lacking IFN-γ show lower adipose tissue inflammation and better glucose control. Therefore, there is an interaction between different immune cells that must be further eluted.

Lymphoid cells of innate immunity (ILCs) are recognized as an innate analogue of T cells due to similar functionality. However, they do not miss adaptive antigen receptors of T cells. They are divided into 5 subclasses: killer cells (NK), ILC1, ILC2, ILC3 and lymphocyte tissue inducer cells (LTi). Lymphoid cells of innate immunity protect barrier tissues from pathogens and maintain immune homeostasis in several tissue types. In addition, some of these cells have cytotoxic characteristics that are important for removing the converted cells and keeping macrophages in homeostasis. In a steady state, cytotoxic lymphoid cells kill macrophages of adipose tissue to maintain homeostasis. However, this is worsened by a high-fat diet, leading to an increase in pro-inflammatory macrophages in the adipose tissue of mice and obese humans.

A high-fat diet increases the number of NK cells and the production of pro-inflammatory TNF in adipose tissue. A decrease in the production of NK cells reduces macrophages of adipose tissue, inflammation and insulin resistance. In addition, a high-fat diet promotes the proliferation of lymphoid cells in adipose tissue and promotes a pro-inflammatory environment for macrophages through IFN-γ secretion.

Similarly, H. Wang et al. [15] found that obese people had a higher number of lymphoid cells in adipose tissue and blood, which decreased after bariatric surgery. Therefore, NK cells and lymphoid cells seem to contribute to the obesity phenotype by promoting a pro-inflammatory environment.

The results of research by a group of scientists led by F.M. Wensveen [16] showed that obesity increases the activity and proliferation of NK cells, which stimulated the production of IFN-γ. This, in turn, stimulated the differentiation of macrophages and contributed to insulin resistance.

On the contrary, as described by J.R. Brestoff et al. [17] A high-fat diet reduced the number of lymphoid cells in adipose tissue. They are important for maintaining metabolic homeostasis in adipose tissue and for preserving macrophages in the macrophage phenotype.

A.B. Molofsky et al. [18] proved that IFN-γ suppressed the activity of lymphoid cells. Combined, several recent studies point to the involvement of lymphoid cells in inflammation (adipose tissue), potentially creating an unknown immunological trigger that triggers a pro-inflammatory environment. Nevertheless, the results obtained in the study of congenital lymphoid cells still remain unproven in order to draw reasoned conclusions.

Tumor necrosis factor, which is primarily expressed and secreted by macrophages in adipose tissue, was one of the first cytokines to be shown to be elevated in adipose tissue and in the blood of humans by diabetes mellitus and obesity. Expression of tumor necrosis factor in adipose tissue was inversely correlated with insulin sensitivity in obese people without diabetes compared to healthy people. Interestingly, the infusion of tumor necrosis factor in rats impaired insulin sensitivity on the first day. In addition, mice deficient in tumor necrosis factor and its receptors were protected from diet-induced insulin resistance. Neutralization of tumor necrosis factor by infusion of reactive immunoglobulins in rats improved insulin glucose uptake.

G.S. Hotamisligil et al. [19] In their studies, they showed that weight loss in obese people improved insulin sensitivity and reduced the expression of tumor necrosis factor in adipose tissue, suggesting a key role for obesity in inflammation and insulin sensitivity. M.Y. Donath [20] and B. Trinh [21] in different years, based on their studies, proposed to inhibit tumor necrosis factor for the treatment and prevention of type 2 diabetes mellitus.

Studies by I. Nieto-Vazquez et al. [22] examine the mechanism underlying the alarming effect of insulin on tumor necrosis factor. In addition, in the islets of the pancreas, the production of tumor necrosis factor by macrophages leads to dysfunction of insulin-producing beta cells and can directly mediate insulin resistance of pancreatic beta cells. Therefore, tumor necrosis factor plays a decisive role in the development of insulin resistance in several tissue types with high glucometabolic significance.

Adipose tissue macrophages are the primary source of the pro-inflammatory cytokine IL-6, with an estimated contribution of 15-35% of the total circulating IL-6. In particular, V. Mohamed-Ali et al. [23] measured the concentration of IL-6 in arterial and venous blood from subcutaneous adipose tissue. They found twice as much IL-6 in venous blood compared to arterial blood, indicating that most of the circulating IL-6 is excreted from adipose

tissue. Surprisingly, they found no increase in tumor necrosis factor between both types of vessels. In addition, it has been confirmed that most of the IL-6 (including tumor necrosis factor) secreted from adipose tissue comes from macrophages.

Studies by J.J. Senn et al., S. Franckhauser et al. and I. Nieto-Vazquez et al. showed that chronically elevated levels of IL-6 reduce insulin sensitivity in vitro [24], cause hyperinsulinemia in mice, and mediate insulin resistance in mouse muscle tissue. IL-6 increases the activity of cytokine signaling suppressor 3 (SOCS3), which inhibits several downstream messengers of insulin receptor signaling. Interestingly, knocking out the receptor for IL-6 in immune cells did not protect against insulin resistance, but disrupted immune homeostasis in mice, suggesting a finely tuned mechanism.

In the pancreas, the IL-6 receptor is primarily expressed in the endocrine portion, with higher levels in alpha cells. IL-6 expression was increased in pancreatic islets in obese mice and is associated with alpha cell expansion, a well-known histological observation in human islets of type 2 diabetes mellitus. Indeed, inhibition of IL-6 in obese mice inhibited alpha cell expansion accompanied by decreased insulin secretion and stimulated Glucose (GSIS). In addition, administration of IL-6 to mice increased insulin secretion by increasing glucagon-like peptide 1 (GLP1) from intestinal L cells and pancreatic alpha cells. Thus, IL-6 has physiological effects on pancreatic islets, but the underlying mechanism has not yet been revealed.

The pro-inflammatory cytokine IL-1β has been implicated in the development of obesity and type 2 diabetes. Mice with the IL-1 receptor are protected from glucose intolerance caused by high-fat content and inflammation of adipose tissue. However, IL-1β has been shown to play a physiological role in glucose metabolism. Feeding increased the secretion of IL-1β from peritoneal macrophages in a glucose-dependent manner, which promoted insulin secretion. The absence of endogenous IL-1β reduces insulin. Therefore, although IL-1β plays a physiological role in glucose metabolism, chronically elevated levels can lead to the development of type 2 diabetes.

In the pathogenesis of type 2 diabetes mellitus, pancreatic islets are infiltrated by pro-inflammatory macrophages that stimulate the production of IL-1β via NLRP3 inflammases. Initially, IL-1β in low concentrations may be beneficial in promoting β cell proliferation; however, chronically elevated concentrations can lead to beta-cell failure. Administration of the IL-1 receptor antagonist improved glucose tolerance by improving human beta cell function and systemic inflammation.

In addition, chronic administration of IL-1β is capable of causing insulin resistance in adipose tissue in vitro. The mechanisms by which IL-1β mediates insulin resistance have been associated, at least in part, with the downregulation of the insulin substrate-1 receptor (IRS-1) and the aberrant activity of NF-ϰB transcription factors during obesity or inflammatory conditions. Thus, IL1β plays a physiological role in glucose metabolism with harmful effects after chronic exposure to high concentrations.

Macrophages play a crucial role in liver inflammation. Hepatic macrophages are activated and thereby alter the inflammatory pathways in obesity. In addition, there is a marked increase in the liver's infiltration of macrophages (and other immune cells). This leads to the production of inflammatory cytokines that generate insulin resistance in hepatocytes and cause diseases associated with type 2 diabetes mellitus, such as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). However, a recent study in mice and obese humans could not confirm that obesity per se causes a pro-inflammatory phenotypic switch in liver macrophages, even though their depletion prevents diet-induced insulin resistance. Interestingly, liver macrophages have been shown to contribute to the development of insulin resistance regardless of the production of inflammatory factors. Rather, liver macrophages have been shown to produce insulin-like growth factor-binding protein 7 (IGFBP7), which directly alters insulin receptor signalling in the liver.

Thus, the analysis of the literature data indicates an active role of lymphocytes and cytokines both in the development of metabolic syndrome and its manifestation. Immunological changes, which have been identified by the results of numerous experimental and clinical studies, indicate an important role in the development of complications of type 2 diabetes mellitus and obesity. Of particular importance in this aspect is acquired as a result of the support of a long-term chronic inflammatory process, a characteristic metabolic disorder. In this aspect, possible changes in the intestinal microflora in patients with obesity and type 2 diabetes mellitus should also be taken into account. This, in turn, can also be associated with the effect on the immunological system of the body.

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