Review paper

Adipose tissue – component of the immune system

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Abstract

Adipose tissue has so far been considered exclusively as "energy storage". At present, it is an important element of the body, which also takes part in regulation of immunological processes. It was determined that the cells of the tissue – adipocytes – have the capacity of producing adipocytokines. It was also evidenced that adipocytes feature many specific receptors, among which also TLR receptors were described, which affect the activity of the immune system. Furthermore, adipose tissue contains immune system cells, such as macrophages, as well as lymphocytes B, T and their subpopulations.

***Key words**: adipose tissue, adipocytes, adipocytokines, immune system.*

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Adipose tissue characteristics

Adipose tissue is not just an "energy storage", but an active endocrynic organ affecting immunological processes and metabolism of the body [1-4]. It was evidenced that adipocytes – adipose tissue cells – have the capacity of producing and secreting many biologically active substances referred to as adipocytokines (Table 1), among which there are not just cytokines, but also substances of the nature of enzymes, hormones and growth factors [1, 3, 4]. Adipocytokines have act in a pleiotropic manner, having auto- and paracrynic effect on adipocytes, although they also have an endocrynic effect on other tissues and organs [1, 5, 6]. They also have the capacity of modulating the immunological response as a result of affecting the immune system cells. Some adipocytokines, such as IL-6 or PAI-1 (plasminogen activator inhibitor 1), directly cause the inflammatory process, while others have an intermediate effect, as in the case of CRP, protein the expression of which was recorded in hepatocytes stimulated with IL-6 originating from adipocytes [5, 7]. Present studies evidenced that adipose tissue is not uniform. Depending on the location in the body, they differ with the capacity to secrete adipocytokines, as well as cellular composition with varied phenotype, as well as the quantity and proportion of adipocytes forming it, blood vessel stromal cells and immune system cells [7, 8]. In the human body, one may differentiate two basic types of this tissue: visceral and subcutaneous adipose tissue [7]. Both types of this tissue are characterised with production of a unique profile of adipocytokines (Table 1). In the tissue visceral, for example, higher concentrations of IL-6 and PAI-1 are observed, which are secreted to the portal vein system, from where, reaching the liver, they impact on its functions. In turn, in the subcutaneous tissue, there is a higher concentration of leptin and adiponectin, which are released to the circulatory system, affecting the cells of the entire body [7]. Furthermore, differences between these types of the tissue refer to the cellular composition, principally as regards immune system cells. It turned out that visceral adipose tissue surrounding the spleen, stomach, pancreas, and colon, also referred to as omentum, is richer with macrophages, lymphocytes B, as well as dendritic cells and NKT cells [8-10]. Leucocytes of this tissue are also organised in structures referred to as milky spots (MSs), distributed on the peritoneum [8] and are responsible for gathering bacteria and harmful substances from the peritoneal cavity, and affect stimulation and inhibition of immunological response. Also in the mesenterium of mammals, including humans, fat-associated lymphoid clusters (FALC) were discovered, distributed along blood vessels [8, 11]. In

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Table 1. Characteristics of adipocytokines

Adipocytokine name	Place of synthesis	Selected functions	Literature
Adiponectin	adipocytes, skeletal muscles cells (cardiac myocytes), epithelial cells and other	shaping immunological response by secretion of cytokines and inhibition of activation of e.g. NF-κB; participation in autoimmunological processes; impact on proliferation and maturation of adipose tissue cells	[3]
Leptin	adipocytes, placenta, bone marrow, stomach, skeletal muscles, brain	neurocrinic and haematopoietic effect; increase of cytokine production, chemotaxis of PMN cells and proliferation and maturation of T and NK cells	[3]
Resistin	adipocytes (mice), muscles, pancreas, macrophage (humans)	participation in adipocyte differentiation and maturation, regulation of cytokine level; pro-inflammatory and hyperglycaemic effect, and impact on stellate cell of the liver	[3, 17]
Visfatin (NAMPT)	adipocytes, lymphocytes, bone marrow cells, muscle and liver cells	impact on sensitivity to insulin by inhibition of apoptosis, induced production of some cytokines and co-stimulating particles	[18]
Omentin	adipocytes, small intestine, lungs, heart	increased effect of insulin in glucose metabolism, participation in tumours, reproductive system diseases and obesity	[3, 17]
Cartonectin	adipocytes	participation in inflammatory and immunoregulatory processes – by reduction of secretion of IL-6 and TNF, stimulating effect on proliferation of mesenchymal chondroprogenitor cells and suppression to NF-κB	[12]
VASPIN	adipocytes	participation in inflammatory processes and suppression of TNF, leptin and resistin production	[7, 19]
RBP4	adipocytes	participation in retinol supply to tissues	[20]
Adipsin	adipocytes (mice) MN cells (humans)	participation in processes related to obesity	[3, 17]
Plasminogen activation inhibition factor PAI-1	adipocytes, thrombocytes, epithelial cells	suppressive effect on fibrynolysis process, participation in formation of obesity and diseases of circulatory system and diabetes	[9]
Angiotensinogen	adipocytes	stimulation of expression of chemotactic factors, participation in angiogenesis and generation of hypertension	[9]
CRP protein	adipocytes, liver	participation in inflammatory processes and stimulation of LDL quantities	[9]
Lypocalin 2	adipocytes, macrophages	impacts on insuline resistance and inflammation through secretion of TNF in adipocytes	[7]
Protein ANGPTL2	adipocytes	participation in local inflammation	[7]
TNF	adipocytes	participation in generation and development of inflammation	[7]
IL-6	adipocytes, liver, muscles	participation in obesity in humans and mice, and in generation of type 2 diabetes	[7]
IL-18	adipocytes	participation in inflammation, obesity and atherosclerosis	[7]
CCL2	adipocytes, stromal vessel cells	participation in recruitment of monocytes to the inflammation site and in glucose management	[7]
CXCL5	stromal vessel cells, macrophages	participation in insulin synthesis on the JAK-STAT pathway	[7]
SFRP5	adipocytes	participation in inhibition of inflammatory process	[7]

these structures, a new lymphocyte subpopulation was discovered [8, 11], referred to as natural T helper lymphocytes (nT_H2). Such lymphoid clusters, although less numerous, are also present in subcutaneous adipose tissue. Moreover, it was evidenced that adipose tissue is present around internal organs, such as the heart or kidneys. Furthermore, adipose tissue cells – adipocytes – were also identified in bone marrow, lungs, and the adventitia of major blood vessels [7].

It was evidenced that high-calorie diet can promote the development of a pro-inflammatory state in these depots in a similar manner to that observed in subcutaneous and visceral adipose tissue. On this basis, also adipose tissue was differentiated as: perirenal, epicardial, pulmonary, periadventitial, and of bone marrow [7].

Characteristics and role of adipocytes in immunity

Typical adipose tissue cells – adipocytes – are characterised with small content of cytoplasm, because most are composed of one (uniocular) or several (polyocular) fat drops. Moreover, it was evidenced that the cells are rich in mitochondria providing them with energy during many metabolic transformation occurring within them [4]. Adipocytes feature many receptors in charge of their sensitivity to external stimuli, including interaction i.a. with the immune system [1, 6, 7]. Among receptors expressed in the adipose tissue cells, playing an important role in the immunity of the body, TLR receptors must be listed [12, 13]. Such markers are capable of recognising pathogens and initiating inflammation, therefore these particles constitute an important element of natural immunity [13]. In mesenchymal cells of the stem of immature adipose cells, TLR1-6 and TLR9 expression was evidenced [12]. In turn, in preadipocytes, as well as mature adipocytes, expression of TLR1-9 was identified, which are in charge of stimulation of cytokine production as a result of antigen recognition [12, 13]. It was also evidenced that the receptors on such cells, can regulate their differentiation, as well as impact on differentiation and function of adipocytes [12]. What was, however, surprising, was the fact that preadipocytes are capable of quicker reaction (in hour 4) than mature adipocytes, as a result of LPS recognition by TLR4, and secretion of pro-inflammatory factors such as IL-6, chemokines CCL2, CCL5 and CCL11 [12]. It was also evidenced that pro-inflammatory factors, generated as a result of chronic stimulation with LPS, have a negative impact on maturation and differentiation of preadipocytes [12]. Such data indicate that cytokines released during infection, such as IL-6, TNF, IL-1β, IL-8 and CCL2, are mainly products of preadipocytary origin, not deriving from adipocytes. In turn, adipocyte stimulation with LPS, the activation of which occurs via TLR4, leads to NFκB induction [12, 13]. It was also evidenced that LPS not only activates adipocytes via TLR4 receptor, but also via TLR2. However, it was stated that TLR2 expression is directly affected by resistin [12], while adiponectin is a factor regulating expression of the entire range of TLR receptors, which have inhibiting effect on their secretion, and activating effect onto NFκB signal pathway [12, 13]. It was evidenced that TLR receptors are expressed in different time of adipocytes differentiation, as e.g. TLR2 occur in the early phase of adipocyte maturation, while TLR9 – in late phase [12]. Moreover, expression of receptors TLR1, 4 and 6 in cells belonging to the stromal vascular fraction (SFV) was recorded [6, 12, 13]. Also, in epithelial cells of the adipose tissue, expression of TLR 5, 7, 8, 9 and even receptor TLR10 was recorded [12, 13], hence it is assumed that TLR receptors of the adipose tissue are an important element deciding on the participation of this tissue in immunological response.

Immune system cells in the adipose tissue

Adipose tissue is principally composed of adipocytes, yet it also includes immune system cells, such as macrophages and lymphocytes [7, 8, 14, 15], the composition and proportions of which differ depending on the location of the adipose tissue in the body.

Macrophages present in the adipose tissue constitute about 10% SVF (stromal vascular fraction) [1, 6, 7, 13]. The cells are present in larger quantities in visceral adipose tissue than in subcutaneous adipose tissue. It was evidenced that macrophages of the adipose tissue reveal approximately 30% genetic similarity to preadipocytes [1, 7, 13], which suggested that macrophages building the adipose tissue may also be generated as a result of preadipocyte differentiation [1, 12, 15]. The present study showed that the macrophages are formed as a result of transformation from monocytes that infiltrated the adipose tissue from the circulatory system [7, 13]. It was also evidenced that, both in humans and in mice, the quantity of macrophages in the adipose tissue correlates with the fat mass [4, 6, 15]. It was observed that infiltration of monocytes from the circulatory system is contributed by adipocytes which by secreting chemotactic monocytes (MCP-1), macrophage migration inhibition factor (MIF-1), macrophage inflammatory proteins (MIP-1α), chemokine CCL5 (RANTES) and macrophage colony stimulating factor (M-CSF), support diversification and maturation of monocytes [7, 13]. It was also recorded that macrophages of the adipose tissue produce TNF which by inducing NFκB pathway causes inhibition of preadipocyte maturation, while in adipocytes causes lipolysis during which palmitic acid and stearic acid are released, which induce TLR4 receptors and activate NFκB in macrophages, which in turn leads to the development of inflammation [7,13]. It was evidenced that in adipose tissue, there are two populations of macrophages with M1 and M2 phenotypes. In overweight people, in adipose tissue, there are principally macrophages with M1 phenotype, namely classically activated macrophages, while in slim people, mainly heterogenic fraction of macrophages is observed with M2 phenotype [7]. It was also evidenced that M1 macrophages are formed as a result of stimulation with cytokines produced by lymphocytes Th1 (e.g. IFN-γ) and as a result of LPS, which stimulates macrophages to secrete pro-inflammatory cytokines (TNF, IL-6) [7]. In turn, macrophages of M2

phenotype are formed after stimulation with IL-4, IL-13 secreted by Th2 lymphocytes, causing intensification of anti-inflammatory cytokine production (IL-10) and weakened generation of pro-inflammatory agents [7]. Hence, these macrophages are considered as cells related to repair of damaged tissues and alleviation of inflammatory condition [7].

Lymphocytes in adipose tissue are represented by T and B lymphocytes [7, 8, 14, 16]. Populations of lymphocytes T in this tissue differ with location and effect on metabolism, while their quantity is related to the body's fat mass. It is suspected that the greatest impact on the relation between the fat mass and the accumulation of T lymphocytes is due to leptin produced by adipocytes, which is responsible for infiltration and proliferation of lymphocytes T [8]. At the same time, it was evidenced that among important factors related to the function of T cells in the adipose tissue is the level of CD3 receptor mRNA, which is related to chemokine RANTES- in charge of T cell activation in the inflammation [8]. It was observed that some T cell subpopulations have a regulatory effect on the phenotype of macrophages that build the adipose tissue. And so, regulatory T cells (T_{reg}) $CD4^+$ and Th2 helper cells, present in majority in adipose tissue in slim people, by inhibition of pro-inflammatory macrophages, show protective effect onto the body [7, 8]. These cells also have a regulatory effect on the growth in adipose tissue mass and expression of TNF-α and IL-6. In turn, effector T cells $CD8^+$ and cytokines produced by Th1 helper cells impact on macrophage activation in the adipose tissue and development of pro-inflammatory cytokine cascade [14]. Also, Th17 helper cells [8], principally present in visceral tissue, although also in subcutaneous and circumrenal tissue, are a subpopulation of lymphocytes principally related to autoimmunological processes in the adipose tissue and growth of fat mass [8]. It is worth mentioning that in adipose tissue, there are newly described natural Th2 lymphocytes (nT_H2). It was evidenced that such cells produce cytokines characteristic of Th2 helper cells, namely IL-4, IL-5, IL-10, and IL-13, and that their main function is related to participation in the course of allergic processes and in defence of the body during invasion of various parasites [11].

B cells are present in majority in visceral adipose tissue, and are principally represented by B1 subpopulations. It was evidenced that B1 cell response related to pathogens is quicker than that of B2 cells, and the antibodies produced by them have a more pleiotropic effect [8]. Therefore, regulation of B1 cells by nTh2 cells can improve immunity to infections caused by such pathogens. It was evidenced that B1 cells are the main source of IL-10 in the adipose tissue, as well as T15 antibodies e.g. in the course of infection with *Streptococcus pneumonia* [8]. Moreover, it was evidenced that B1 cells are present in large quantities in milky spots (MSs) of the peritoneum, which ensures quicker immunological response to bacterial products such as LPS that may infiltrate the abdominal cavity [8].

Conclusion

Increasingly more data testify to the fact that the adipose tissue is an active endocrynic organ which takes part in the control of inflammatory process by secreting many biologically active adipocytokines. Furthermore, the identified expression of TLR receptors in cells building the adipose tissue and evidencing the presence of effector cells of the immune systems (macrophages, T and B cells) in this tissue is also a testimony of the important role of adipose tissue in immunity.

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