Review paper

Adipocytokines affecting the immune system – selected data

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Abstract

The paper describes adipocytokines – biologically active substances produced by the adipose tissue, which affect the immune system. Adipocytokines include such substances as leptin, adiponectin, resistin, adipsin, visfatin, VASPIN, cartonectin, angiotensinogen, lipocalin 2, ANGPTL2 protein, TNF, IL-6, IL-18, CCL2 and SFRP5, that are characterized below.

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

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Introduction

Adipocytokines are biologically active substances principally produced by adipose cells – adipocytes, although their synthesis was also recorded in other cells of the human body. The adipocytokine group includes not only cytokines, but also substances such as enzymes, hormones and growth factors. Such substances have an auto- and paracrynic effect on adipocytes producing them, although they also have an endocrynic effect on other tissues and organs [1-3]. They also have the capacity of modulating the immune response as a result of effect on the immune cells. Among adipocytokines affecting the immune system, the following must be listed: lectin, adiponectin, resistin, adipsin, visfatin, VASPIN, cartonectin, angiotensinogen, lipocalin 2, ANGPTL2 protein, TNF, IL-6, IL-18, CCL2 and SFRP5.

Leptin is 16 kDa protein, principally produced by adipocytes, but also by the placenta, stomach, skeletal muscles and brain, that are less important source of this substance [1, 4, 5]. The role of this adipocytokine is principally related to modulation of the immune response and appetite control, although also to the functioning of the neuroendocrynic system and energy homeostase, haematopoiesis and angiogenesis [1, 5]. Leptin is considered as pro-inflammatory cytokine that indicates common structural and functional properties with IL-6, IL-2 and granulocyte colony-stimulating factor (G-CSF) [1, 5, 6]. The studies evidenced that its concentration grows due to the "ejection" of large quantities of pro-inflammatory cytokines during the acute phase of inflammation and as a result of LPS stimulation during infection. Moreover, its amount in the human body correlates with the amount of adipose tissue [1, 4]. Leptin takes part in activation of monocytes and macrophages, causing their proliferation and increase pro-inflammatory cytokine levels (TNF, IL-6, IL-12, CCL2) [3]. Moreover it was evidenced that it activates neutrophils by stimulation of CD11b receptor expression, as well as other immune cells, owing to increased activation of receptors such as CD25 (IL-2R) and CD71 [1, 4, 5]. Furthermore, it affects different stages of neutrophil phagocytosis such as chemotaxis and the process of absorption, and impacts on differentiation and cytotoxicity of NK cells. It also stimulates proliferation of T lymphocytes towards Th1 lymphocytes, and protects them against apoptosis. It is assumed that during the acute phase of inflammation, leptin may be treated as acute phase protein originating from the adipose tissue, that support the immune system [4].

Adiponectin is a protein composed of 244 aminoacids produced almost exclusively in the adipose tissue [1, 4, 6, 7]. In trace amounts, it is also synthesised in skeletal muscle cells, e.g. cardiac myocytes and epithelial cells. It belongs to the family of C1q/TNF factors, because it reveals high structural homology with the family of proteins characterised with the amino-terminal collagen-like region, as well as carboxy-terminal complement factor C1q-like globular domain. Furthermore, the globular domain of this protein reveals similarity to the family of TNF ligands [1, 4, 6, 7]. Adiponectin in serum occurs in long, native form with low molecular

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weight, that can create dimers or trimers. Moreover it can occur as complexes with medium (hexamers) and high molecular weight, as well as in globular forms [8]. The cytokine acts via AdipoR1 and AdipoR2 receptors, which are present in all tissues, although type 1 is much more prevalent in skeletal muscles, while type 2 in liver. Moreover, native and globular forms of adiponectin have different affinity to such receptors – AdipoR1 receptor is specific for the globular form of the protein, while AdipoR2 – for the native form. Despite the fact that adipocytes are the main source of this cytokine, its concentration is inversely proportional to the body weight and insulin level, but proportional to HDL level [7, 8]. *In vitro* studies evidenced that synthesis of adiponectin in adipocytes was inhibited by TNF and IL-6, which may explain its lower level in obese people [5, 8]. Contrary to other adipocytokines, it reveals anti-inflammatory and anti-sclerotic effect [5, 8]. When TNF-α synthesis is decreased, adiponectin inhibits the macrophage response during the inflammation and their phagocytic activity. In this conditions this substance blocks also activation of NK-κB in epithelial cells [5, 8]. Adiponectin reduces expression of inter-cellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells, thus reducing diapedesis of the circulating monocytes. Its properties are also related to inhibition of IL-6 production as a result of induced synthesis of anti-inflammatory IL-10 [1, 4, 7]. It was, however, recorded that in some conditions adiponectin may also reveal pro-inflammatory properties, because it may increase synthesis of CXCL88 chemokines in monocytes and macrophages as a result of stimulation with LPS [1, 5]. It may also induce apoptosis in monocytes and increase activity of AMPK kinase (AMP-activated protein kinase), as well as inhibit expression of "scavanger" receptors in macrophages [1, 4, 5].

Resistin is 12.5 kDa protein, containing high quantities of cysteine. Its expression in animals was principally observed in the adipose tissue. In turn in humans, only a small quantity of resistin is produced in adipocytes, while the majority – in monocytes and macrophages [1, 4, 5]. It belongs to the family of resistin-like molecules (RELM), also defined as FIZZ (found in inflammatory zone), which are connected with regulation of inflammatory processes. *In vitro* studies evidenced that macrophage stimulation with LPS or pro-inflammatory cytokines (IL-1, IL-6 and TNF) leads to considerable increase in resistin production during infection. In turn, IFN-γ and lectin do not affect its level [1, 4]. It was indicated that resistin enhances insulin-resistance and has a hyperglycemising and pro-inflammatory effect, as well as suppressive effect on adipocyte maturation and diversification. It also stimulates endothelial cells to secrete such substances as monocyte chemoattractant protein-1 (MCP-1), VCAM-1 and ICAM-1, which indicates that it is adiponectin antagonist [1, 4, 5].

Adipsin is produced in adipocytes and mononuclear cells in humans, while in animals – exclusively in the adipose tissue. In human this substance correspond to complement factor D, which take places in activation of alternative complement pathway [1, 6].

Visfatin, also known as pre B cell colony-enhancing factor (PBEF), is principally produced by adipocytes, although also by macrophages of the visceral adipose tissue, and in small quantities by subcutaneous adipose tissue [1, 5, 9-11]. The visfatin mRNA expression significantly increases during differentiation preadipocytes to adipocytes. This adipocytokine reveals potent pro-inflammatory properties, e.g. activates leukocytes and stimulates production of such cytokines as TNF-α, IL-1β and IL-6 [9, 11]. Furthermore, it has an unfavourable effect on the activity of vascular endothelium by increasing NF-κB activity in such cells, which in turn leads to increased expression and production of pro-inflammatory cytokines like IL-6 and IL-8, and adhesion molecules (ICAM-1, VCAM-1 and E-selectin) [9, 11]. Moreover it inhibits neutrophil apoptosis via mechanisms associated with kaspase 3 and 8 [1, 5, 9].

Visceral adipose tissue-derived serine protease inhibitor (VASPIN), is an adipocytokine deriving from the serine protease inhibitor family. It is produced by cells occurring in subcutaneous and visceral adipose tissue [5, 12]. It was recorded that higher expression of this factor positively correlates with increased leptin level, while negatively – with higher adiponectin expression. Studies indicate that VASPIN might also have anti-inflammatory effects, as it suppresses the production of TNF-α and IL-6 [5, 12].

Cartonectin (CTRP-3- C1q/TNF-related protein-3) is produced by adipose cells as a result of stimulation with LPS. It acts as inhibitor of immune cells causing decreased synthesis of IL-6 and TNF [7, 12, 13]. Moreover, it was evidenced that this adipocytokine inhibits NF-κB activation [7, 12, 13].

Angiotensinogen, that is produced by adipocytes, affects the course of phagocytosis and monocyte infiltration to the inflammation site [2]. Furthermore, it has a stimulating effect on the expression of adhesion molecules ICAM-1 (inter-cellular adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule 1), as well as chemoattractants like MCP-1 (monocyte chemoattractant protein 1) and M-CSF (macrophage colony-stimulating factor), by which it affects leukocyte mobility and migration [2].

Lipocalin 2 (neutrophil gelatinase-associated lipocalin) is principally produced by adipocytes and macrophages [4]. It belongs to pro-inflammatory adipocytokines, which lead to induction of inflammation by increasing NF-κB activity and TNF secretion by adipocytes. Serum concentration of lipocalin 2 are positively associated with CRP levels [4].

ANGPTL2 protein is principally produced by adipose cells, although its low concentration was also recorded in plasma [4]. It was evidenced that overexpression of this protein results in the exacerbation of local inflammation in adipose tissue. Moreover, it was observed that this adipocy-

tokine in epidermis contributes to the development of inflammation by affecting attachment of leukocytes to blood vessel walls, and increasing their permeability [4]. Furthermore, ANGPTL2 stimulates the immune response by activation integrin signalling in endothelial cells, monocytes and macrophages [4]. It was also evidenced that decrease in the synthesis of this protein leads to inhibition of the inflammation by decreased production of pro-inflammatory cytokines by adipocytes [4].

Tumor necrosis factor (TNF) is a pro-inflammatory adipocytokine produced by monocytes and macrophages present in adipose tissue [1, 4]. The cytokine affects generation and development of the inflammation by NF-κB activation in macrophages [1, 4].

Interleukin 6 (IL-6) is produced i.a. in adipose tissue, as well as in liver and muscles [1, 4, 10]. It was evidenced that adipocytes are the source of 30% of this cytokine in the body.Interleukin belongs to pro-inflammatory cytokines, which can directly cause inflammation in adipose tissue. Moreover it can also cause inflammation in hepatocytes, but via mechanism associated with CRP protein [1, 4, 10].

Interleukin 18 (IL-18) is a pro-inflammatory adipocytokine also produced by adipocytes [4]. Overexpression of this cytokine results in increased production of adhesion molecules in endothelial cells, and increased macrophage infiltration to the inflammation site [4].

Monocyte chemotactic protein (MCP-1) – CCL2 [chemokine (C-C motif) ligand 2] is produced by adipocytes and stromal cells [4]. This protein belongs to pro-inflammatory cytokines contributing to the development of inflammation by participation in monocytes recruitment [4].

Secreted frizzled-related protein 5 (SFRP5) is a recently discovered anti-inflammatory cytokine produced by adipose tissue [4]. *In vitro* studies indicated that it is antagonist of WNT5a (wingless-type MMTV integration site family, member 5A) [4], responsible for activation of JNK (C-Jun N-terminal kinase) [4], and thus for production of pro-inflammatory cytokines in macrophages. Therefore, decreased expression of SFRP5 load to macrophages accumulation and increased production of pro-inflammatory cytokines (TNF and IL-6) in adipose tissue [4].

Conclusion

Described above adipocytokines are biologically active substances that modulate immune responses. The mechanism of this modulation is related to regulation of pro- and anti-inflammatory factors production and activation of immune cells. Thus in many cases adipocytokines decide the maintenance of homeostasis in immune system.

References

1. Fartuzzi G (2005): Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 115: 911-919.
2. Lau DC, Dhillon B, Yan H et al. (2005): Adipokines: molecular links between obesity and atheroslcerosis. Am J Physiol Heart Circ Physiol 288: H2013-H2041.
3. Kershaw EE, Flier JS (2004): Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 89: 2548-2556.
4. Ouchi N, Parker JL, Lugus JJ, Walsh K (2011): Adipokines in inflammation and metabolic disease. Nat Rev Immunol 11: 85-97.
5. Tilg H, Moschen AR (2006): Adipocytokines: mediators linking adipose tissue, inflamation and immunity. Nat Rev Immunol 6: 772-783.
6. Niedźwiedzka-Rystwej P, Deptuła W (2009): Adipose tissue and immunity system. Alergia Astma Immunologia 15: 101-105 (in Polish).
7. Schäffler A, Schőlmerich J, Salzberger B (2007): Adipose tissue as an immunological organ: Toll-like receptors, C1q/TNFs and CTRPs. Trends Immunol 28: 392-399.
8. Owecki M (2009): Adiponectin, and the adiponectin paradox in human metabolism. Przegląd Kardiodiabetologiczny 4: 42-48.
9. Varma V, Yao-Borengasser A, Rasouli N, et al. (2007): Human Vistatin expression: relationship to insulin sensitivity, intramyocellular lipids, and inflammation. J Clin Endocrinol Metab 92: 666-672.
10. Orlik B, Handzlik G, Olszanecka- Glinianowicz M (2010): The role of adipokines and insulin resistance in the pathogenesis of nonalcoholic fatty liver disease. Post Hig Med Dośw 64: 212-219 (in Polish).
11. Moschen AR, Kaser A, Enrich B, et al. (2007): Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. J Immunol 178: 1748-1758.
12. Poulos SP, Hausman DB, Hausman GJ (2010): The development and endocrine functions of adipose tissue. Mol Cell Endocrinol 323: 20-34.
13. Wölfing B, Buechler C, Weigert J, et al. (2008): Effects of the new C1q/TNF-related protein (CTRP-3) "cartonectin" on the adipocytic secretion of adipokines. Obesity 16: 1481-1486.