Adipokines

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Contributor: Frommer Klaus

Adipokines are adipose tissue-derived factors not only playing an important role in metabolism but also influencing other central processes of the body, such as inflammation.

Keywords: adipokines ; adipocytokines ; rheumatic diseases ; rheumatoid arthritis ; autoimmunity

1. Introduction

Disorders affecting the joint can be divided in two central groups. Primary inflammatory autoimmune arthritides consist of rheumatoid arthritis (RA) and spondyloarthritides, including psoriatic arthritis (PsA) and ankylosing spondylitis. Findings in inflammatory arthritis are often compared to non-autoimmune osteoarthritis (OA). OA is usually induced by previous joint injury, biomechanical stress on joints due to malposition, or overweight and obesity. Metabolic diseases, such as diabetes or hyperlipidemia, are considered key risk factors for OA development[1]. Though cartilage degradation is a central feature of OA, resulting in an inflammatory response due to mechanical joint damage, the whole joint is affected, including adjacent bone, which involves the formation of osteophytes[1]. In contrast, RA is an autoimmune disorder characterized by severe chronic inflammation early within the disease, leading to irreversible joint damage if left untreated[2]. RA affects mainly peripheral joints symmetrically, leading to progressive joint damage. The clinical presentation of RA varies, and environmental factors and epigenetic mechanisms have been associated with this disorder[3][4]. A persistent inflammatory infiltration of the synovial tissue contributes to local synovial cell activation, which causes the release of pro-inflammatory and matrix-degrading factors to the tissue and joint space. RA synovial fibroblasts (RASFs) exhibit an autonomous activated phenotype contributing to the inflammatory milieu as well as synovial hyperplasia [4][5].

PsA and RA are both rheumatic chronic inflammatory diseases sharing similarities such as synovitis but also differences in the pathophysiology. This includes a different vascular pattern in the affected joints[6], a less pronounced synovial hyperplasia in PsA compared to RA patients [7], and the cell infiltrates at the inflamed synovial–entheseal complex being more prominent in PsA patients[8]. Therefore, enthesitis is one of the frequent features of PsA according to the Classification of Psoriatic Arthritis (CASPAR) criteria[9][10] but rare in the case of RA as well as OA. PsA patients also respond differently to treatment. For example, the anti-IL17A biologic secukinumab is more effective in PsA than in RA patients.

Dysregulation of immune-endocrine circuits is involved in the development of chronic metabolic disorders, such as obesity, metabolic syndrome, and diabetes, but also plays a role in chronic inflammatory diseases, such as RA[11]. Understanding the mechanisms of both immune regulation and resolution of inflammation is crucial for the development of successful treatment approaches to achieve and maintain remission or low disease activity in RA and PsA.

2. Adipose Tissue and Adipokines

Adipose tissue is the key tissue regulating energetic homeostasis. It also serves as an endocrine organ due to secretion of a large number of bioactive substances. The factors that are released by adipose tissue are called adipocytokines. This group of mediators includes adipokines, cytokines, chemokines, complement factors, and hormones[12]. Cytokines produced by an excess of adipose tissue can affect the whole body, leading to the development of a so-called low-level inflammation, which can be observed in obese individuals.

Adipokines are factors mainly produced by adipocytes in the white adipose tissue. Adipose tissue secretes a large number of highly biologically active factors. However, many adipokines such as leptin and adiponectin are also known modulators of immune responses. Systemic alterations of adipokines have been identified for a large number of chronic inflammatory diseases, and the potential of adipokines such as adiponectin and leptin has been discussed. Therefore, adipokines have been investigated for many years in the context of chronic inflammatory and degenerative rheumatic diseases

systemically as well as on the local level in cells and tissues. Furthermore, pro- and anti-inflammatory properties of adipokines have been identified. Therefore, it has been accepted in the past years that adipokines play an important role in immune-mediated rheumatic disease and degenerative OA.

2.1. Adiponectin

Adiponectin, encoded by the *ADIPOQ* gene, has been described as a mainly anti-inflammatory adipokine. Adiponectin is produced in large amounts by adipocytes of the white adipose tissue[13]. Adiponectin concentrations are inversely correlated with the body mass index (BMI). Adiponectin is a complex molecule. Adiponectin monomers form different isoforms, depending on the degree of oligomerization: the trimer (low molecular weight (LMW)), the hexamer (middle molecular weight (MMW)), and the multimeric (high molecular weight (HMW)) adiponectin consisting of 12–18 monomers. Globular adiponectin, consisting of the monomeric head-domain, is formed by proteolytic cleavage. The monomer occurs as an intermediate in adipocytes, while in the circulation the main forms are the multimeric adiponectin isoforms. Besides the two main adiponectin receptors, AdipoR1 and AdipoR2, which are able to bind globular and full-length adiponectin isoforms with different affinities, other receptors such as T-cadherin and PAQR3 (progestin and AdipoQ receptor family member 3) have been described[12][13][14][15][16][17]. Recently, Tanaka and colleagues showed that adiponectin overexpression increased the regeneration of myofibers promoting muscle regeneration in a T-cadherin-dependent manner[17]. Adiponectin has several central biological functions, such as fatty acid biosynthesis and inhibition of gluconeogenesis within the liver[12][13][15]. However, adiponectin not only shows potential as a biomarker due to the systemic alterations under inflammatory condition, which were found to decrease[18][19][20] or increase[21][22][23] in physiological and pathophysiological conditions, but is also actively involved in inflammatory responses and affects different cell types. In type 2 diabetes, atherosclerosis, and metabolic syndrome, predominantly anti-inflammatory effects have been described[12][18][24]. However, in the context of rheumatoid arthritis, the role of adiponectin is not fully understood. On cellular and tissue level, opposite effects have been described for rheumatic diseases, such as RA, where it seems to promote inflammation and tissue damage in the affected joints. Recent findings will be outlined in the sections below.

2.2. Leptin

The main adipokine produced by adipocytes is leptin. Leptin concentrations are positively correlated with white adipose tissue mass. In addition, leptin has central functions in metabolism and also plays a role in inflammation and inflammatory disorders[25]. Leptin is encoded by the *LEP (ob)* gene and is a 16 kDa non-glycosylated protein. The effects of leptin are mediated by binding to the long form of the leptin receptor LEPR[26]. By inducing anorexigenic factors, leptin is known to be a central protein in appetite regulation and obesity. However, leptin is also involved in many processes besides insulin secretion and basal metabolism, such as reproduction, bone mass regulation, and (chronic) inflammatory diseases[14][25]. Leptin, in turn, is induced in adipose tissue, depending on the energy status, by sex hormones and by inflammatory mediators[14][25]. In contrast to adiponectin, leptin is considered a pro-inflammatory adipokine. It is involved in low-grade inflammation due to overweight in obesity[26]. Both the innate and adaptive immune responses are affected by leptin, and the LEPR is expressed at the surface of most immune cells. Leptin increases the phagocytosis of macrophages, induces proliferation of monocytes and macrophages, alters the cytotoxicity of natural killer cells as well as the proliferation of CD4 T cells, suppresses type 2 T helper cells (Th2), and increases Th1 responses as well as regulatory T cell (Treg) responses[25][27]. Leptin itself is induced by pro-inflammatory cytokines during acute infection and sepsis, but it is also induced during chronic inflammatory autoimmune diseases[25][28].

2.3. Visfatin

Visfatin, or pre-B-cell colony-enhancing factor (PBEF), is a multifunctional protein that has the ability to promote B cell differentiation and possesses nicotinamide phosphoribosyl-transferase (Nampt) enzymatic activity. These different mechanisms of action make visfatin a very interesting protein. Whether altered local visfatin levels are associated with its extracellular interaction with cells or due to its intracellular enzymatic Nampt activity, leading to changes in the nicotinamide adenine dinucleotide content, remains to be clarified. Visfatin is produced by adipose tissue as well as other tissues, such as liver, bone marrow, and muscle. It can be induced by pro-inflammatory factors, chemokines, hypoxia, and visfatin itself, and in turn visfatin induces a pro-inflammatory response in many cell types and tissues by itself[12][15][24]. The cell surface receptor for visfatin is unknown, and several studies have shown that the visfatin effects are in part due to its Nampt activity[14]. However, an interaction with insulin-like growth factor (IGF)-1 signaling has been reported. Here, it can been shown that visfatin inhibits IGF-1-mediated function independently of the IGF-1 receptor activation[29], suggesting another mechanism of action besides its Nampt activity. Interestingly, it has been recently observed that

several micro RNAs (miRNAs) are involved in the visfatin-mediated effects specifically in the context of OA chondrocytes[30]. Visfatin significantly reduced viability and induced apoptosis in OA chondrocytes, involving the NFκB pathway as well as decreasing miR-140 and miR-146a and increasing iR-let7e expression in this study[30].

2.4. Resistin

Resistin is a homodimeric cysteine-rich protein that is mainly produced by macrophages in humans, whereas in animals such as mice, the source of resistin is the adipose tissue resident adipocytes[14][31]. Therefore, results from animal studies can often not directly be translated to the human situation. Human resistin was described to be a mainly pro-inflammatory protein promoting immune cell recruitment and immune cell activation[14][32] because it is produced by macrophages. Furthermore, a role in the context of the development of, for example, coronary artery disease, atherosclerosis, type 2 diabetes, as well as OA and psoriasis has been reported[14][33], showing a mainly inflammation-promoting effect. However, anti-inflammatory effects of resistin have also been described on cellular and tissue level[31]. Therefore, the effect of resistin may depend on the tissue and pathophysiological condition studied. In addition, an immunomodulatory role in the context of rheumatic diseases, including RA, PsA, and OA, has been described[14].

2.5. Chemerin, Vaspin, and Omentin

Chemerin precursors consist of a hydrophobic signal peptide sequence, a cysteine fold-containing domain, and a labile C domain. Chemerin is activated after hydrolization by cysteine or serine proteases. Removal of the signal sequence leads to a secreted preform with low biological activity. Different cleaved isoforms and underlying mechanisms of cleavage have been described in the past years[34], which are in the focus of current investigations. Chemerin is involved in immune responses, and its role in coronary atherosclerosis and metabolic syndrome development, among other diseases, has been described[14]. Mainly anti-inflammatory chemerin properties have been described for macrophages as well as in an LPS-induced acute lung injury mouse model[35]. On the cellular level, chemerin acts as a chemoattractant for natural killer cells, macrophages, and dendritic cells[14][36].

Vaspin belongs to a family of serine protease inhibitors. Vaspin has been associated with insulin resistance and metabolic syndrome as well as atherosclerosis and cardiovascular disease[37]. Besides subcutaneous adipose tissue, vaspin is also expressed and produced in other tissues such as skin and skeletal muscle. Interestingly, vaspin has been described to be involved in skeletal muscle inflammation[38]. Vaspin overexpression in mice showed altered metabolism and inflammation with improved glucose tolerance and resistance to high-fat diet-induced obesity with lower systemic IL-6 levels[14]. On the cellular level, vaspin alters adipocyte differentiation and glucose homeostasis. In the context of coronary atheromatous plaques, the pro-inflammatory phenotype of macrophages was suppressed by vaspin[14]. However, limited knowledge regarding the evaluation of the specific role of vaspin in the context of autoinflammation in RA is available.

Omentin is a glycoprotein that binds to galactofuranosyl residues of microorganisms and to the lactoferrin-binding protein. It is expressed mainly in omental adipose tissue. However, omentin is abundant in the plasma of healthy donors[39]. Omentin has been described to mainly have anti-inflammatory effects. Anti-atherogenic effects in obese individuals have been described, as well as a negative association with inflammatory bowel disease and metabolic syndrome[14][39].

2.6. Progranulin, Lipocalin-2, and Nesfatin

Progranulin (PGRN, granulin/epithelin precursor) consists of seven granulin/epithelin repeats that can be cleaved into small homologous subunits. Full-length protein as well as the resulting peptides after cleavage are biologically active[40]. PGRN is an autocrine factor promoting different physiological processes, such as chondrocyte differentiation and proliferation as well as enchondral ossification[14]. Pro- and anti-inflammatory effects of PGRN have been described. The anti-inflammatory properties are mainly mediated by competitive binding to tumor necrosis factor (TNF) receptors disturbing the TNFα-mediated responses[25][41]. PGRN is produced by many different cells such as adipocytes, macrophages, and chondrocytes and has been suggested as a potential biomarker in inflammatory disease[42].

Nesfatin (nesfatin-1) is an adipokine involved in satiety induction and in energy homeostasis. It is secreted by the hypothalamus and acts as an anorexigenic factor. In addition, it is produced by subcutaneous adipose tissue and other tissues within the gut, pancreas, and testes[43]. Lipocalin-2 (LCN2) is an adipokine induced by pro-inflammatory factors, such as IL-1beta, LPS, and other cytokines, as well as dexamethasone and other adipokines, such as leptin and adiponectin[14][44][45].

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