Review

The role of tissue "environmental" adipokines in the pathogenesis of rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterised by persistent synovial inflammation, joint destruction, and functional disability. The disease aetiology is multifactorial, involving genetic, environmental, and immunological components. Recent research has highlighted the significant role of metabolic factors in modulating inflammatory pathways in RA. Among these, adipocytokines, bioactive molecules secreted by adipose tissue, have emerged as key mediators linking metabolism and immune responses. Adipocytokines such as leptin, adiponectin, resistin, and visfatin not only regulate energy homeostasis but also as tissue "environmental" molecules influence immune cell activity and cytokine production. Their dysregulated expression in RA patients suggests a potential role in disease pathogenesis and progression. Understanding the complex interplay between adipocytokines and inflammatory mechanisms in RA may open new avenues for targeted therapeutic strategies and biomarkers for disease activity.

Introduction

Rheumatoid arthritis (RA) is the most common form of chronic, autoimmune, inflammatory joint disease, leading to cartilage and bone destruction and subsequent joint remodelling (1). The full aetiology of the disease is unknown. It is believed to arise from the interaction of genetic factors and environmental factors, including epigenetic factors (2, 3).

The pathological process in RA is defined by inflammation and hyperplasia of the synovial membrane, proliferation of granulation tissue (pannus), and elevated levels of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumour necrosis factor-alpha (TNF-α) (4, 5). Alongside erosive synovitis, the disease is characterised by diffuse inflammatory involvement of other organs and systems, such as the skin, lungs, cardiovascular system, and others, related to the higher mortality in these subsets of patients (6, 7).

Patients with RA have a higher cardiovascular risk due to proven common pathogenetic mechanisms between atherosclerosis and rheumatic diseases, which are based on pro-inflammatory cytokines such as IL-1) and TNF-α (8, 9).

White adipose tissue, adipocytokines (resistin, leptin, and adiponectin) and inflammation

It has been proven that white adipose tissue (WAT) represents an endocrine organ that produces and secretes molecules with cytokine-like properties, called "adipocytokines" (10). Although they have endocrine, autocrine, and paracrine effects, adipocytokines participate in various physiological and pathological processes, and their synthesis is associated with a state of "mild inflammation" in patients with increased body mass index (BMI) (11). Adipocytokines are involved not only in regulating eating behaviour and energy balance but also the inflammation and immune responses as tissue "environmental" molecules (12, 13). In the recent years, their role in the pathogenesis of rheumatic diseases such as RA and osteoarthritis (OA) has been proven, through modulating the inflammatory process in the joints, disrupting the balance between catabolic and anabolic factors, and remodelling bone and joint cartilage (14). For example, the chronic inflammatory process and

elevated levels of pro-inflammatory cytokines in RA lead to the so-called "wasting syndrome," characterised by a significant reduction in body cell mass.

In this case, rheumatoid cachexia is accompanied by increased fat mass and stable weight. More than 50% of patients are characterised by rheumatoid-cachectic obesity, for which adipocytokines play a role (15). Adipocytokines include resistin, leptin, adiponectin, and visfatin. Adipose tissue in the human body is divided in two main types: WAT and brown adipose tissue (BAT).

The main function of the WAT is to serve as energy storage. In the last decades multiple studies aimed to prove the additional endocrine function of WAT to synthesise numerous chemical substances (cytokines, chemokines, hormonal factors). In humans WAT has two subtypes, subcutaneous and visceral fat. There are several key distinctions between visceral WAT and subcutaneous WAT. The visceral WAT exhibits higher insulin resistance, with adipocytes that are more metabolically active and display increased lipolytic activity. The visceral WAT holds more macrophages in comparison to subcutaneous WAT (16). The abundance of visceral WAT is a major risk factor for the developing of type 2 diabetes.

WAT mainly consists of adipocytes, but it also includes a variety of other cell types such as pre-adipocytes, immune cells, fibroblasts, and vascular cells. Together, these non-adipocyte components make up what is referred to as the stromal vascular fraction. The quantity and characteristics of these cells differ depending on the specific fat depot and vary between individuals with obesity and those without. In lean individuals, WAT typically contains immune cells with regulatory and anti-inflammatory properties. These include M2-like adipose tissue macrophages (ATMs), regulatory T cells (Tregs), T helper type 2 (Th2) cells, invariant natural killer T (iNKT) cells, and eosinophils. In the conditions of obesity adipocytes store increased amounts of lipids, resulting in hypertrophy and hypoxia, called adipose tissue disfunction (17).

In such tissue environment the adipocytes start to synthesize proinflammatory cytokines and chemokines, TNF-α, IL-6, IL-8 and monocyte chemoattractant protein (MCP)-1. A major difference in the cell structure between lean WAT and adipose WAT is the distribution of the macrophages. As a rule, macrophages are evenly scattered, whereas in obese state macrophages gather around apoptotic adipose cells. In general, the inflammation is a process, which includes energy loss and energy intake reduction in direct and indirect manner. In this setting the wasting syndrome (excessive loss of weight, without changes in the diet) presents in many inflammatory diseases (18).

The process of adipose tissue inflammation has its unique distinction, which allows the coexistence of inflammation and overweight in obese individuals. Interestingly, the proinflammatory mediators in WAT (TNF-α, MCP-1, IL-6) originate from the activated adipose tissue macrophages. IL-4 plays an important role for the local macrophage proliferation in the adipose tissue. This process happens near the so called 'crown structures', surrounding the necrotizing adipocytes, leading to local increase in the number of the M2 macrophage in WAT (16).

In this proinflammatory environmental tissue condition the phenotype of the adipose tissue macrophages is polarized to inflammatory state. In comparison, in lean, insulin-naïve mice the adipose tissue macrophages secrete anti-inflammatory cytokines such as IL-10 and arginase 1, while in the adipose tissue of obese animals the expression of proinflammatory cytokines such as TNF-α and (inducible nitric oxide synthase) iNOS is far greater (19, 20).

The role of the macrophage in the pathogenesis of inflammation

Another important factors in the pathogenesis of inflammation are the macrophages (21). Macrophages are highly plastic cells that originate from the peripheral blood monocytes. When the monocyte penetrates different type of tissue, it differentiates into different macrophages. According to the surrounding environment the macrophages polarise into two main subtypes, M1 (classically activated macrophages) and M2 (alternatively activated macrophages).

Microbial lipopolysaccharides (LPS) and interferon (IFN)-γ promote the macrophage to become the M1 subtype, whereas IL-4 and IL-13 stimulate the M2 subtype polarisation. Important factors for the polarization of M1 macrophages are hypoxia-inducible factor (HIF-1α) and the reactive oxygen species (ROS) (22). M1 macrophages show affinity in inflammatory conditions with secretion of pro-inflammatory substances such as IL-1, IL-6, IL-12 and TNF-α. Furthermore, M1 macrophages synthesise large amounts of ROS and reactive nitrogen species (RNS) helping them in the processes such as phagocytosis, pathogen killing and clearance of damaged and degraded cells.

Studies have shown that M2 macrophages exhibit anti-inflammatory properties by secreting IL-10, IL-4, transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF) (22, 23). M2 macrophages exhibit important immunomodulatory function as they can inhibit the T-cell proliferation and activation and participate in the T helper 2-type immunity response. The abundance of M2 macrophages promote tissue remodelling, regeneration and fibrosis (23, 24).

Role of the M1/M2 macrophages in RA

In RA the predominant subtype is of M1 macrophages, which secrete pro-inflammatory cytokines and stimulate the disease progression. They are associated with early inflammatory lesions, higher disease activity and exacerbation of the symptoms and signs of the disease (25). In contrary, the increased number of M2 macrophages is linked to lower disease activity and reduction of the symptoms, due to the secretion of anti-inflammatory cytokines (26, 27). Studies found a positive correlation between the macrophage number in synovial tissue and the hyperplasia of the synovium, the disease activity score (DAS) 28 and erosions in patients with RA (28).

Inflammatory mediators such as TNF-α, IL-6 and IL-1β have significant role in promoting the polarization of the macrophages towards M1 subtype, such as the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signalling pathway. A crucial role in this process plays the transcriptional factor STAT3. IL-6-induced STAT3 activation leads to upregulation of receptor activator of nuclear factor kappa-B ligand (RANKL) in osteoblasts (29, 30).

Adipokines and their functional roles

Resistin

Resistin is known as an adipose tissue-specific factor (ADSF). It is a cysteine-rich protein (31). Its molecule was discovered in 2001 (32). Initially, it was believed that resistin is secreted only by adipose tissue cells and plays a role exclusively in insulin resistance and the onset of type 2 diabetes.

Later, it was proven that in humans, resistin has more immunoregulatory functions and is predominantly secreted by immunocompetent cells, particularly mononuclear leukocytes and macrophages, with correlations between serum resistin levels and the degree of subclinical inflammation (33, 34).

In mice resistin is predominantly synthesised in adipose tissue, whereas in the human body only a low level of resistin was found in the adipocytes. In humans resistin is expressed in bone marrow, synovial fluid, synovial tissue and circulating blood. Different studies showed that proinflammatory mediators such as TNF-α, IL-1β, IL-6, or lipopolysaccharide (LPS) stimulate the synthesis and secretion of resistin in peripheral blood mononuclear cells (PBMCs). Some authors proved, that within the adipose tissue, resistin could promote the expression the same pro-inflammatory cytokines and the activation of the nuclear factor kappa-B (NF-κB) pathway (35).

The pro-inflammatory effects of resistin are mediated through intracellular activation of the NF-kB signalling pathway, where direct or indirect stimulation of NF-kB translocation from the cytoplasm to the nucleus is observed. NF-kB is a transcription factor that induces the expression of many pro-inflammatory genes, such as the genes for IL-1, IL-6, and TNF-α (36).

Leptin

Leptin is a 16-kDa non-glycosylated peptide hormone secreted by adipocytes, which plays a key role in energy balance by regulating appetite and increasing energy expenditure in the human body (37).

Leptin belongs to the type-I cytokine superfamily and has a structure similar to IL-2, IL-6, and granulocyte colony-stimulating factor (G-CSF) (38). Normal leptin levels are important for maintaining and regulating immune system functions. Leptin has both anti-inflammatory and pro-inflammatory properties. Elevated leptin levels during infection or inflammatory reactions induce and maintain T-cell function and immune responses. On the other hand, leptin stimulates the production of cytokine antagonists to regulate the body's immune responses (39).

Leptin is a potential modulator of both the innate and adaptive immune responses by stimulating the activation and proliferation of various types of immune cells, by mediating the production and secretion of proinflammatory cytokines, by preventing the apoptosis of neutrophils, eosinophils and dendritic cells (40).

Leptin stimulates the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-12 and induces the expression of adhesion molecules on the surface of monocytes and macrophages (39, 41). In neutrophils, leptin stimulates chemotaxis through the MAPK (p38 mitogen-activated protein kinase) signalling pathway, while in eosinophils, it enhances the secretion of surface molecules such as intercellular adhesion molecule (ICAM)-1 and CD18, as well as pro-inflammatory cytokines such as IL-1β, IL-6, and IL-8 (42, 43).

In recent years, it has been proven that leptin acts as a pro-inflammatory cytokine during immune reactions and body defence and plays an important role in the pathogenesis of chronic inflammation and immune-mediated musculoskeletal diseases such as RA. Leptin increases the proliferation of Th17 cells, B-cell activity, and the production of TNF and IL-6 by macrophages in RA. Leptin activates the migration of fibroblast-like synoviocytes and the secretion of IL-8, as well as the expression of nitric oxide synthase (NOS)-2 and adhesion molecules in chondrocytes, which is followed by lymphocyte infiltration and degradation of joint cartilage (44).

Adiponectin

Adiponectin is a 244-amino acid protein, adipokine, with a molecular weight of about 26kDa, which is predominantly secreted by the adipocyte of WAT. Adiponectin plays an important role in cellular processes such as energy metabolism, insulin sensitivity, and inflammation. Adiponectin exerts its biological effects through interaction with cell surface receptors AdipoR1 and AdipoR2. T-cadherin is the non-signalling receptor for adiponectin. AdipoR1 and AdipoR2 are expressed on the surface of most cells, including monocytes, B cells, and NK cells (45, 46).

Adiponectin plays an important role in modulating inflammatory responses. It has been shown that adiponectin reduces the inflammatory response in macrophages, inflammation in endothelial cells, muscles, and epithelial cells via activation of cyclic adenosine monophosphate (cAMP) signalling and increase of AMP-activated protein kinase (AMPK) activity. Adiponectin reduces the production of oxidative stress mediators and suppresses inflammatory responses. It decreases the secretion of C-reactive protein (CRP) and suppresses signalling pathways involving NF-kB and TNF-α (46, 47).

The stimulation of inflammatory mediator secretion through the activation of synovial fibroblasts expressing adiponectin receptors is the basis of the hypothesis stating the pro-inflammatory properties of adiponectin in rheumatic diseases such as RA and OA (48).

Visfatin

Visfatin, previously known as pre-B cell colony-enhancing factor, is a 52-kiloodalton cytokine. Its gene is lo-

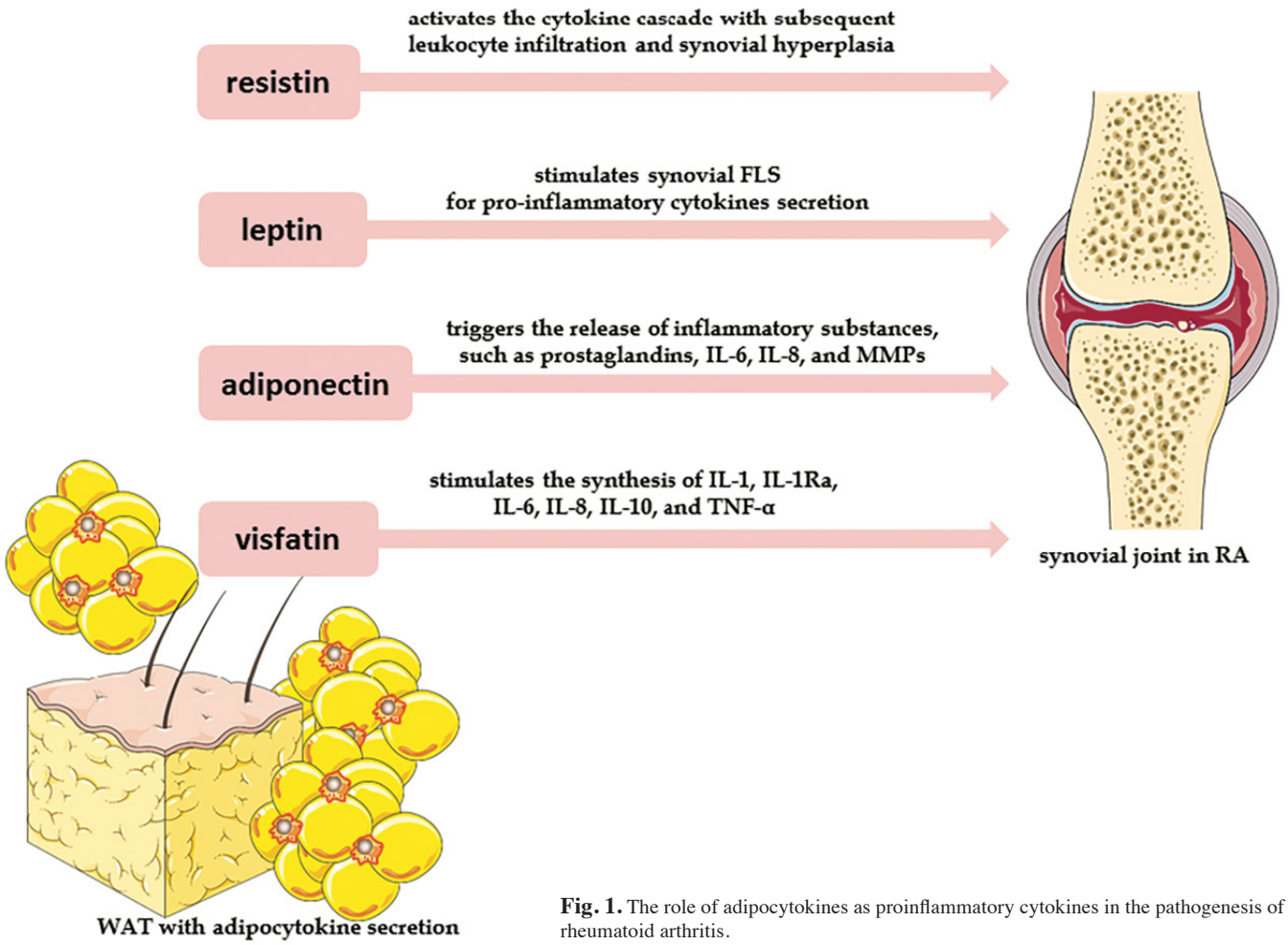

Fig. 1. The role of adipocytokines as proinflammatory cytokines in the pathogenesis of rheumatoid arthritis.

cated on chromosome 7q22.2. Visfatin has proven effect on obesity and insulin resistance (49, 50).

Visfatin is also produced by the muscle cells, bone marrow, liver, placenta, heart and kidney. Back in the day when it was discovered, it was thought that in was synthesized by lymphocytes, acted on lymphocyte maturation and that his function was mainly immunomodulatory, connected with the release of inflammatory mediators (51-54).

Visfatin is highly expressed and secreted in number of inflammatory diseases such as RA, OA, cardiovascular disease and inflammatory bowel disease (55).

Role of adipocytokines in the pathogenesis of RA

Although there is sufficient data on the pathogenic role and altered levels of adipocytokines in the blood of patients with RA, it is unclear whether they contribute to the development of the disease, or they are nonspecific markers of inflammation (56). Figure 1 synthetises the proinflammatory role of resistin, leptin, adiponectin and visfatin in the cytokine production, cell activation and synovial inflammation in RA (Fig. 1). The role of individual adipocytokines as "tissue environmental" factors contributing to the pathogenesis of RA will be discussed in detail below and is summarised in Table I.

Role of resistin in RA pathogenesis

The role of resistin in the pathogenesis of RA has been studied for years. Tarkowski *et al*. have shown that resistin competes with LPS for binding to Toll-like receptor 4 (57). In an *in vitro* experiment with peripheral blood monocytes and synovial leukocytes, Bokarewa *et al*. demonstrated that resistin stimulates the secretion of TNF-α, IL-6, and IL-1, responds to changes in TNF-α levels, increases its own secretion through positive feedback, and induces arthritis upon intra-articular injection (58).

TNF-α, but not IL-6 or IL-1β, stimulates cells to secrete resistin. It has been shown that resistin tightly regulates cytokine synthesis and provides an alternative pathway for cytokine network activation even in the absence of TNF-α. This is associated with the insufficient effect of TNF-α therapy in some RA patients and the lack of effectiveness after intra-articular injection of TNF-α inhibitors (59). The intra-articular injection of resistin into a healthy mouse knee activates the cytokine cascade with subsequent leukocyte infiltration and synovial hyperplasia. The injected amount is comparable to resistin levels in synovial fluid in RA patients during acute joint inflammation. Resistin levels in synovial fluid are higher in patients with inflammatory than in those with non-inflammatory joint disease. The authors showed that resistin accumulates in synovial fluid

Table I. Environmental adipocytokines and their role in rheumatoid arthritis.

Type of adipocytokine	Stimulators for synthesis	Effect	Role in RA	References
Resistin	TNF-α, IL-1β, LPS, IL-6	Activation of NF-κB, synthesis of TNF-α	Activation of the cytokine cascade with subsequent leukocyte infiltration and synovial hyperplasia	Silswal *et al*. (36) Otero *et al*. (56) Bokarewa *et al*. [(8)
Leptin	TNF-α, IGF-1	Stimulation of the activation and proliferation of monocytes and macrophages, phagocytosis, neutrophil chemotaxis, activates the migration of fibroblast-like synoviocytes	Stimulation of synovial fibroblast-like synoviocytes in RA to produce pro-inflammatory cytokines	Ait Eldjoudi *et al*. (44) Otero *et al*. (56) Lee *et al*. (63)
Adiponectin	AMPK activators IL-10, IGF-1, FGF21,	Reduction of the production of oxidative stress mediators, suppresses inflammatory responses, decreases the secretion of C-reactive protein, suppresses signalling pathways involving NF-kB and TNF-α	Trigger the release of inflammatory substances like prostaglandins, interleukin-6, interleukin-8, and matrix metalloproteinases	Targońska-Stępniak *et al*. (65) Łączna *et al*. (77)
Visfatin	TNF-α, IL-6, IL-1β, HIF-1α,	Lowering of the blood glucose	Production and secretion of IL-1, IL-1Ra, IL-6, IL-8, IL-10, and TNF-α.	Brentano *et al*. (79) Robinson *et al*. (85)

TNF-α: tumour necrosis factor; LPS: lipopolysaccharide; NK-κB: nuclear factor κB; IGF-1: insulin-like growth factor; AMPK-AMP: activated protein kinase; FGF21: fibroblast growth factor 21; HIF-1α: hypoxia-inducible factor 1-alpha.

in RA patients, while circulating protein levels in peripheral blood remain low. This is linked to increased local synthesis of resistin in synovial fluid or its preferential accumulation at inflammation sites (59).

Possible mechanisms for the increased local concentration of resistin in synovial fluid include the presence of different leukocyte populations in the two compartments, the presence of intra-articular resistin-inducing substances, and the elimination or inactivation of resistin from circulation. High levels of resistin have been found in human bone marrow cells, known to be an important source of inflammatory cells infiltrating the synovial membrane during arthritis. Resistin levels correlate with the number of intra-articular leukocytes and IL-6 levels. Reilly *et al*. showed that plasma resistin levels correlate with inflammatory markers such as CRP, IL-6, and TNF receptor 2 in metabolic diseases, while Senolt *et al*. confirmed this correlation only for CRP and erythrocyte sedimentation rate (ESR) in RA patients (34, 60).

Senolt *et al*. conducted the first study on the relationship between serum resistin levels and levels in synovial fluid and synovial tissue in RA patients compared to OA and seronegative spondyloarthropathies (SpA) patients. They found higher resistin expression in the sublining layer of the synovial membrane in RA patients compared to the control groups. Resistin expression was found in synovial fibroblasts and some types of inflammatory cells infiltrating the rheumatoid synovial membrane, such as macrophages, B lymphocytes, and plasma cells, but not in T lymphocytes. The authors concluded that the affected joints are the main site of resistin secretion, and synovial fluid resistin levels may indicate both the intensity of inflammatory infiltrates in synovial tissue and the number of inflammatory cells in synovial fluid. Serum resistin levels are more closely associated with systemic inflammation and disease activity in polyarticular involvement, while synovial fluid levels reflect the inflammatory process in the joint itself (34).

Supporting Schaffler *et al*. research, age, body mass, and gender do not affect resistin levels, further proving that in humans, resistin is primarily related to the inflammatory process rather than obesity and insulin resistance (59).

By immunohistochemistry double staining for resistin and alkaline phosphatase, Krumbholz *et al*. have shown that resistin is localised along with osteoblasts at sites of newly formed, non-mineralized bone tissue and bone erosions in RA patients. This indicates that resistin may play a role in osteoblast differentiation and activation of osteoblasts (61).

Increased resistin levels were found in RA synovial fluid compared to synovial fluid from patients with non-inflammatory rheumatic diseases. Resistin levels correlated with the disease activity and acute phase reactants (CRP, ESR, IL1-Ra), which further supports the role of resistin in the inflammatory process of RA (62).

Role of leptin in RA

Leptin is the adipocytokine most strongly associated with RA. The increased systemic levels of leptin correlate with the disease activity, and it has been shown that leptin stimulates synovial fibroblast-like synoviocytes to produce pro-inflammatory cytokines, such as TNF-α and IL-6, as well as CC-chemokines (63, 64). Furthermore, leptin supports a Th1-dominant immune response by promoting Th1 cell differentiation and suppressing Th2 cell responses.

Most studies demonstrate elevated leptin levels in individuals with RA; however, some investigations have reported either no significant change or even lower levels compared to healthy individuals or those with OA (65).

The pro-inflammatory activity of leptin leads to the release of inflammatory mediators in the synovium, where the synovial cells synthesize matrix metalloproteinases (MMPs) and RANKL connected with bone and cartilage de-

struction (66). Interestingly, leptin levels are elevated in RA patients, but synovial fluid levels are lower than plasma levels, indicating local consumption of leptin in the joints (67, 68).

Olama *et al*. evaluated the ratio between leptin levels in serum and synovial fluid, which is significantly higher in RA patients and correlates with disease duration, disease activity, levels of pro-inflammatory cytokines, and acute-phase reactants (69). Additionally, it has been shown that obese RA patients have increased leptin production, which correlates with the presence of anti-citrullinated protein antibodies (ACPA), indicating leptin's potential role as a modulator of the humoral immune response (70).

In RA, leptin levels can be used as a systemic biomarker to monitor the long-term effects of the biological therapy on body mass and appetite, aiming to maintain energy homeostasis during the remission of RA (71). An interesting study measured the serum leptin level in RA patients and its correlation with clinical manifestations and disease activity. The results showed that there was no significant correlation between serum leptin levels and the duration of the disease. A possible explanation could be that serum leptin level in chronic inflammation is reduced opposite to the leptin serum level in acute inflammation (72).

Role of adiponectin in RA

Adiponectin is the adipocytokine with the highest levels in the circulation. Unlike other adipocytokines, adiponectin levels are low in obese patients, type-2 diabetes, and metabolic syndrome, but circulating adiponectin levels are elevated in inflammatory conditions such as RA, and its local levels in synovial fluid are higher in RA compared to OA (73).

Adiponectin is generally recognised as an anti-inflammatory adipokine in conditions such as obesity, type 2 diabetes, metabolic syndrome, and atherosclerosis, where elevated levels are thought to offer protective benefits. Physical exercise enhances the synthesis and release of adiponectin, contributing to better regulation of glucose and lipid metabolism. This may help to explain why individuals with obesity tend to have reduced adiponectin levels (74). However, in the context of RA, adiponectin appears to have pro-inflammatory properties, particularly in joint tissues. It can trigger the release of inflammatory substances like prostaglandins, IL-6, IL-8 and MMPs. Research has also linked adiponectin to joint damage and radiographic progression in RA. A study conducted by Targońska-Stępniak *et al*. investigated the levels of adiponectin and leptin in the blood of a group of 109 RA patients, with additional risk factors as elevated BMI, high glucose levels, elevated lipid profile level. They found a correlation between adipokine levels and BMI, where patients with high BMI have elevated leptin, but normal levels of adiponectin in their blood. In the same study population patients with RA history for more than 10 years showed elevated levels of adiponectin in their blood. Adiponectin concentrations were notably lower in overweight or obese RA patients compared to those with a normal BMI (65). Furthermore, in patients with longstanding RA, physical activity is often limited due to persistent pain, irreversible joint damage, and loss of muscle mass.

In order to prove the connection of adiponectin with the pathogenesis of RA, Zhang *et al*. conducted a study with two groups of participants without any known inflammatory disease. The participants were stimulated with 5 μg/ml human recombinant adiponectin, then peripheral blood mononuclear cells were extracted from the first group (8 participants) and fibroblast-like sinoviocytes extracted from the second group (9 participants). After ELISA analysis the results showed that adiponectin stimulated the production of IL-6, chemokine (C-X-C motif) ligand 1 (CXCL1) and CXCL5 in both cell groups (75).

Recent research indicates that levels of circulating adiponectin are increased in individuals with autoimmune and inflammatory conditions, such as RA. One possible explanation for this seemingly contradictory finding is that adiponectin is suppressed in situations involving low-grade inflammation, like in metabolic syndrome, due to inhibitory signals from fat cells. In contrast, during intense systemic inflammation, as seen in RA, adiponectin levels rise (76).

In order to prove the role of adiponectin as a component of the inflammatory cascade in RA, Łączna *et al*. conducted a study, aiming to examine the expression of adiponectin in different tissues from patients with RA compared to patients with OA. Samples were taken from plasma, bone marrow, synovium and Hoffa's fat pad. The authors concluded that the expression of adiponectin in RA patients was greater than OA patients. Indeed, environmental adiponectin stimulates the synthesis and secretion of pro-inflammatory cytokines in the joint tissue (77).

The role of adipocytokines in clinical practice remains to be clarified. An interesting study of a cohort of overweight patients in Sweden, followed for 29 years, has shown that serum adiponectin levels are an independent risk factor for the development of RA. This indicates that adipocytokine levels can be used in clinical practice alongside autoantibodies in patients with early and/or very early forms of undifferentiated arthritis, who are monitored for the development of inflammatory-type arthritis (78).

Role of visfatin in RA

Different studies indicated the role of visfatin in the production and secretion of different cytokines, involved in the pathogenesis of the systemic inflammatory disease, such as IL-1, IL-1Ra, IL-6, IL-8, IL-10, and TNF-α. The effects of visfatin on the immune cells (up-regulation of inflammatory mediators and human leucocyte activation) are possible via two signalling pathways - p38 and MEK1. Another important merit of visfatin is the inhibition of apoptosis of neutrophils and macrophages via an IL-6/STAT3 pathway, which helps them to survive in different inflammatory conditions (79-81). It is known that T-lymphocytes, monocytes/microphages are the key players in the progression of RA. They increase the secretion of pro-

inflammatory cytokines such as IL-1, IL-6, IL-17, TNF-α, which leads to the characteristic for the disease clinical manifestations (82).

In patients with RA the serum level of visfatin is increased compared to healthy individuals or patients with OA which makes it a possible marker for disease activity (56). Human chondrocytes stimulated with visfatin produce inflammatory cytokines, MMP-3 and prostaglandin E2 (PGE2) (83, 84).

Robinson *et al*. found that visfatin concentration were related to the increased diastolic blood pressure and diabetes as co-morbidity in RA patients with cardio-vascular disease (85). A possible explanation might be that visfatin could have proinflammatory properties influenced by insulin and/or insulin sensitivity via the NF-κB and JNK pathways (86).

Conclusion

It was originally thought that adipocytokines are secreted and expressed by the adipose tissue and play a crucial role mainly in the regulation of the metabolism. In the recent years their connection and contribution in the inflammatory and immune processes is of great interest in the clinical and basic science as tissue "environmental" molecules. Scientific research on the role of adipocytokines as tissue environmental factor contributing to the pathogenesis of RA has been the subject of extensive studies in the global literature over the past 10 years.

We aimed to summarize the role of adipocytokines in the complicated pathogenesis of RA by describing their effects on various immune cells, proinflammatory pathways involved in RA as well as their association with early inflammatory lesions, disease activity and clinical manifestations The data show that the adipocytokines may be used in the future as biomarkers for disease activity and eventually as therapeutic targets. Continued research in adipocytokine interactions and involvement in signalling pathways will help us understand the pathogenesis of chronic inflammatory diseases such as RA in regard of best treatment strategies aiming disease remission.

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