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REVIEW ARTICLE

RESISTIN IN RHEUMATOID ARTHRITIS

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Summary

Rheumatoid arthritis (RA) is a chronic multisystem illness that affects millions of individuals. The primary goal of RA therapy is to improve patients' quality of life by reducing pain severity, preserving or improving functional capability, and decreasing disability. The significance of resistin in the pathophysiology of RA has been explored in recent years, although its role is unclear as it is largely produced by macrophages. In this review, we have analyzed 10 studies from the PubMed site that demonstrate a relationship between resistin levels and the severity of RA.

Key words: Resistin; Rheumatoid arthritis, Adipokines, Cytokines and sverity of disease

Introduction

RA and Adipokines relashionship

RA is defined as a condition characterized by the appearance of anti-citrullinated protein antibodies and rheumatoid factor in the majority of patients (1). It is important to diagnose RA at an early stage, and seek therapy to reduce pain, maintain or increase functional capability, enhance the quality of life of the patient, and avoid disability (2, 3). The idea that the sole role of adipose tissue (AT) is energy storage has been debunked with the identification of the secretory functions of adipokines, which have been the subject of extensive scientific research. Since the discovery of leptin in 1994, several forms of adipokines have been identified and studied. These remarkable proteins play active roles in regulating pathological processes such as metabolism, inflammation, immunity, and more. However, the findings linking adipokines to the development of RA are still contradictory (4, 5). Given the high prevalence of RA and its socioeconomic impact on disability, the aim of our review is to establish a relationship between resistin and the severity of the rheumatoid inflammatory process.

Role of Adipokines in RA

The role of adipokines in RA is significant. Although RA is a prevalent form of arthritis, with a worldwide incidence of 1%, its precise pathogenesis remains unclear. Several discoveries, including Tumor Necrosis Factor

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(TNF) and interleukin, have emphasized the critical role of adipokines in the pathogenesis of RA, providing potential targets for treatment (6-9). Adipokines play a vital role in inflammation and offer unique connections between adipose tissue (AT), adipokines, and RA (10, 11). As a result, both basic researchers and clinicians are interested in this topic. Gómez R *et al.* have demonstrated that adipokines have potent modulatory effects on RA-related tissues and cells, such as bone, cartilage, synovium, and different immune cells (12).

RA and Resistin relashionship

Resistin is a cysteine-rich protein consisting of 108 amino acids known as resistin-like molecules (RELMs) that was originally isolated in rodents (13). In humans, it is mostly derived from macrophages and circulating monocytes (14). Resistin plays a crucial role in linking inflammation and obesity (15, 16). Kassem *et al*. (2010) explored the etiology of RA by examining potential connections between levels of resistin in synovial fluid and serum in radiographic joints of RA patients. Their findings provided evidence in favor of the idea that resistin has a role in RA pathophysiology and recommended serum resistin levels as a useful biomarker of an RA patient's illness prognosis (17). In 2011, Yoshino compared serum resistin levels in RA patients with those in healthy volunteers and found that while serum resistin levels did not differ between the two groups, they were positively correlated with RA patients' CRP levels, indicating pro-inflammatory cytokine activity (17). Similarly, Fadda *et al*. (2013) evaluated resistin levels in the synovial fluid and blood of individuals with osteoarthritis (OA) and RA, and found higher levels in RA patients, suggesting a role for resistin in the etiology of inflammatory rheumatic diseases. However, the authors recommended more research to determine whether resistin is a reliable measure for assessing the development of this illness. High resistin levels in synovial fluid indicate poor prognosis for RA (18) (19), and Kang *et al*. (2013) supported this theory with their findings (20). In RA patients, the researchers discovered a connection between inflammatory markers and resistin levels. Bustos Rivera-Bahena *et al*. (2015) showed that high levels of resistin are strongly linked with clinical symptoms of RA (21). Similarly, a meta-analysis by Huang *et al*. found that patients with RA had significantly higher serum resistin levels than controls (22). However, some studies failed to find variations in synovial fluid and serum resistin levels between patients with RA and healthy individuals or significant correlations between serum resistin and the homeostatic model assessment of insulin resistance (HOMA-IR) (23). After examining resistin levels in RA patients, Al-Kady *et al*. (2010) also found no significant variations in resistin levels between patients in the RA group and the control group (24). Nevertheless, resistin's pro-inflammatory effects have been noted in most research involving RA patients, which suggests it is a reliable indicator of the disease's development.

Cytokines and resistin in RA

Inflammation is mediated by cytokines, which are small cell signaling molecules. When cytokines attach to appropriate cell-surface receptors, they set off intracellular signaling cascades and subsequently change the cell's behavior (25). This may result in the enhancing or blocking of a variety of genes and transcription factors, which might then produce additional cytokines, increase the cellular surface receptors for other chemicals, or block their specific effects through feedback blocking mechanisms. It has been shown that resistin increases vascular cell adhesion molecule and intercellular adhesion molecule-1 to enhance endothelial cell activation. Resistin downregulates TNF receptor-associated factor-3 (TRAF-3) (26). Additionally, it has been proven that resistin causes human endothelial cells to produce pentraxin 3, an inflammatory mediator linked to atherosclerosis (27, 28). It has been revealed that resistin stimulates the production of chemokines and cytokines in human articular chondrocytes (29). Only one study reported how resistin and lipopolysaccharide compete to bind to the receptor of Toll-like receptor 4 (TLR4) in individual epithelial and myeloid cells (30). Activation of TLR sets off a series of internal processes that change NFkB signaling, transcription, and other signaling pathways. Resistin binds to peripheral blood mononuclear cells (PBMCs) and causes cytokine generation. Resistin also binds to the TLR4-transfected (human epithelial kidney cell line (HEK293) RTLR4 promotes the protective inflammatory responses of the host by binding to foreign bacterial and viral components. To learn more about how resistin-induced pro-inflammatory effects in PBMCs are mediated, the authors assessed the function of intracellular signaling pathways. Before resistin stimulation, cells were pretreated with NFkB (mitogen-activated protein kinases) and phosphatidylinositol 3-kinase inhibitors. In a dose-dependent way, inhibition of mitogen-activated protein kinases and NFkB prevented resistin-induced production of TNF-α, IL-6, and IL-1β at both the protein and mRNA levels. In contrast, inhibiting PI3K increased resistin activity. Because PI3K functions as a negative regulator of inflammatory responses induced by TLR (4

and 2), this results in increased production of the cytokines IL-6 and IL-1β (31). These findings suggest that resistin causes pro-inflammatory intracellular signals that are regulated by NF-kB and mitogen-activated protein kinase signaling processes and are most likely initiated when resistin binds to TLR4.

RA causes thickening and hyperplasia of the synovium as a result of the inflammatory process. Numerous inflammatory cells enter the synovium and release pro-inflammatory cytokines such as IL1, IL6, and TNF-α. Blocking these mechanisms has led to the development of highly effective biological therapies for RA (32). The resistin gene is overexpressed in PBMCs, particularly after stimulation with the proinflammatory cytokines IL1 and TNF-α (33). Recent studies have demonstrated a strong correlation between plasma resistin levels and inflammatory indicators such as CRP, TNF receptor 2, and IL6 (34). In RA patients, increased resistin levels in synovial fluid also significantly correlate with inflammatory indicators such as ESR and CRP (35). Resistin upregulates in response to TNFα stimulation and is considered a key molecule that stimulates NF-kB activation and cytokine formation in PBMCs. Furthermore, injection of recombinant mouse resistin into healthy mice's knee joints caused leucocyte infiltration and synovial hyperplasia (36). These findings provide evidence that resistin is a significant cytokine with strong regulatory properties that has a role in the pathophysiology of RA. Interestingly, Kassem *et al*. (2010) suggested that serum resistin levels may be a reliable predictive indicator for RA (17); Thommesen *et al*. (2006) demonstrated the stimulatory effects of resistin on the proliferation of osteoblasts and its elevated expression during the development of osteoclasts, through protein kinase C and PKA signaling systems (37). Numerous research studies have shown the relationship between resistin levels and RA, as shown in Table 1.

Table 1. demonstrates trials investigating the relationship between resistin and RA.

	Type of trial	participants	Conclusion
1	A case control trial (45).	RA and controls.	The study found a significant correlation between resistin level and disease activity, radiographic joint damage, as well as inflammatory indicators such as ESR, RF and CRP. The researchers concluded that resistin can be considered a reliable biomarker for RA.
2	A cross sectional investigation of the relationship between resistin and HOMA-IR (23)	RA	HOMA-IR and resistin do not significantly correlate.
3	A case control study (46).	RA patients and controls.	The study found no variation in serum resistin levels between the two groups. However, patients with RA had significantly higher levels of resistin in synovial fluid compared to controls.
4	A case control trial (47).	RA and controls.	The study found no significant differences in serum resistin levels between the two groups, but it was observed that in RA patients, there was a positive correlation between resistin and CRP levels.
5	Cross sectional investigation of the relationship between inflammatory markers and serum resistin (18).	RA	The study found that resistin levels were significantly higher in patients with RA compared to the controls.
6	A case control trial (48).	RA and healthy subjects.	The study found no significant association between disease activity and serum resistin levels in RA patients compared to healthy subjects.
7	A meta-analysis study was conducted to examine the relationship between RA and adipokine levels (22).	RA	RA patients had considerably greater serum adipokine levels.
8	A case control trail (49).	Patients with RA, spondyloarthropathies (SpA), and OA	The study discovered that the levels of synovial fluid resistin were significantly higher in patients with rheumatoid arthritis compared to those diagnosed with spondyloarthropathies or osteoarthritis. Furthermore, the serum resistin levels in patients with SpA and RA were higher when compared to those with OA.
9	A cross sectional trail (21).	121 patients with RA, divided into low (22), moderate (56), and high (43) severity groups.	The study found a positive correlation between circulating resistin levels and disease activity in patients with RA.
10	Observational study (50).	88 post-menopausal women with rheumatoid arthritis (RA) 42 healthy women as control group.	There was no significant difference in serum resistin levels between the post-menopausal women with RA and the healthy women in the control group.The study was aimed to investigate the association between serum resistin levels and inflammatory markers.

Therapeutic Targeting

Researchers have investigated the ability of cholesterol-lowering agents to reduce resistin levels in patients with T2DM at both the blood and cellular levels. Statins, or HMG-CoA reductase inhibitors, have powerful anti-inflammatory properties in addition to inhibiting a key enzyme in the production of cholesterol in the liver. Although atorvastatin at a dose of 10 mg/day for 6 months was not highly effective, it did lower resistin levels in patients with type II diabetes. Meanwhile, qPCR analysis revealed that atorvastatin therapy decreased resistin mRNA levels in adipocytes and human macrophages/monocytes (38). Similarly, simvastatin effectively suppressed the CRP-enhanced up-regulation of resistin mRNA and expression of protein in different in vitro investigations, which revealed high expression of resistin mRNA in human PBMCs (39). Therefore, interactions between resistin and CRP may contribute to the etiology of atherosclerosis, and statin treatment may reverse these effects. Shyu *et al*. (2009) discovered that atorvastatin inhibited TNF-α-enhanced resistin production in macrophages; the suppression of AP1 transcription factor binding to the resistin promoter and Rac phosphorylation were the mechanisms by which atorvastatin exerted its inhibitory effect. As a result, statin medication may be used as an additional therapeutic approach to manage CVD in people with RA (40). TNF-α mediates the effects of resistin, a pro-inflammatory cytokine (41). Therefore, it is recommended that anti-TNF therapy be investigated in RA patients. Infliximab treatment (an anti-TNF-α monoclonal antibody) significantly decreased levels of serum resistin in patients with RA (42). Similarly, it has been demonstrated that oleic acid lowers the expression of the resistin gene in isolated adipocytes (43, 44). Therefore, therapy aimed at reducing resistin levels in the blood is one way to make use of our developed understanding of the effect of resistin on the onset of RA.

Conclusion

The most crucial areas of research are focused on understanding the specific molecular pathways through which resistin interacts with cells and molecules, as well as the genetic diversity among these mediators. In the long run, identifying novel therapeutic approaches that aim to reduce serum resistin levels may be an effective strategy to prevent negative consequences and develop new treatments for RA.

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Conflict of Interest

None declared.

Ethical Standards

Ethical standards were not applicable in this study.

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