Commentary

Soluble RAGE: a hot new biomarker for the hot joint?

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Abstract

The receptor for advanced glycation endproducts (RAGE) interacts with distinct ligand families linked to the inflammatory response. Studies in animal models suggest that RAGE is upregulated in the inflamed joint and that blockade of the receptor, using a ligand decoy soluble form of RAGE (sRAGE), attenuates joint inflammation and expression of inflammatory and tissue-destructive mediators. In this issue of *Arthritis Research & Therapy*, Rille Pullerits and colleagues reported that plasma levels of sRAGE were reduced in subjects with rheumatoid arthritis compared with healthy controls or subjects with non-inflammatory joint disease. These findings suggest the possibility that levels of sRAGE might be a biomarker of inflammation. Not resolved by these studies, however, is the intriguing possibility that endogenously higher levels of sRAGE might be linked to a lower incidence of arthritis or to the extent of inflammation. Nevertheless, although 'cause or effect' relationships may not be established in this report, fascinating insights into RAGE, inflammation and human arthritis emerge from these studies.

Introduction

In this issue of *Arthritis Research & Therapy*, Pullerits and colleagues [1] reported that plasma levels of soluble receptor for advanced glycation endproducts (sRAGE) were decreased in human subjects with rheumatoid arthritis (RA) compared to healthy normal subjects or subjects with non-inflammatory diseases of the joints (NID). Although no significant differences were observed between levels of synovial sRAGE in subjects with RA and NID, synovial sRAGE levels significantly distinguished those RA subjects treated with disease-modifying anti-rheumatic drugs (DMARDs) from those not on these treatments. Subjects with RA receiving methotrexate displayed significantly higher levels of synovial sRAGE [1]. These fascinating findings, based on a single observation point in each subject, prompt us to consider whether sRAGE's role is cause and/or effect in disease/disease activity in the RA joint.

In this context, full interpretation of these findings will require comprehensive answers to the questions such as the following: Do plasma sRAGE levels vary from day to day in a subject? Do they vary over the lifespan of the individual? What were the levels of sRAGE in the RA subjects before the onset of disease manifestation? What other environmental or genetic factors might influence levels of sRAGE in the individual subject? Despite these caveats, a key lesson in these studies is that levels of sRAGE, at least in the synovial fluid, might be modified by intense anti-inflammatory therapy. Indeed, an emerging theme in the biology of RAGE links this receptor to proinflammatory mechanisms. At least four classes of inflammatory ligands, namely S100/calgranulins, amphoterin (also known as high mobility group box I or HMGB1), Mac-1, and advanced glycation endproducts (AGEs), are signal transduction ligands of RAGE [2-5]. Intriguingly, these ligand families are upregulated in the serum, the synovium or the fluid bathing the arthritic joint. In certain cases, levels of S100/calgranulins and amphoterin, for example, reflect the extent of disease activity [6-9]. Such findings still do not resolve a key issue: is the modulation of plasma sRAGE levels cause or effect? In this context, studies in animal models have provided insights into mechanisms by which RAGE might be linked to proinflammatory mechanisms.

RAGE, inflammation and arthritis: insights from animal models

Experimental findings support the premise that the biology of RAGE extends beyond diabetes [10]. For example, studies in euglycemic mouse models of delayed-type hypersensitivity and colitis in interleukin-10-null mice suggested that a blockade of RAGE attenuated inflammation and the upregulation of cytokines and transcription factors such as NF-κB [2]. In the specific context of arthritis, administration of soluble RAGE to mice with collagen-induced arthritis attenuated clinical scores of joint inflammation, in parallel with

NID = non-inflammatory diseases of the joints; RA = rheumatoid arthritis; RAGE = receptor for advanced glycation endproducts; sRAGE = soluble RAGE.

decreased joint expression of cytokines and antigen/activity of matrix metalloproteinases [11]. In other studies, evidence strongly supporting roles for RAGE ligands in the development of collagen-induced arthritis in mice was demonstrated by a reduced arthritis score and the histological severity of arthritis in animals treated with polyclonal antibodies against amphoterin (HMGB1) [12].

These experiments strongly suggested that augmenting levels of sRAGE was beneficial. Indeed, in the human model, administration of methotrexate resulted in significantly enhanced levels of soluble RAGE in synovial fluid, with a trend toward increased levels in plasma [1]. Presumably, in those subjects, levels of sRAGE rose in parallel with decreased inflammation. It remains unclear whether methotrexate-induced suppression of inflammation facilitated the generation/stability of endogenous sRAGE and, thus, ligand-trapping and reduced inflammation. Alternatively, did inflammation ensue directly as a consequence of endogenously low sRAGE levels – levels that were somehow modulated by administration of methotrexate? Clearly, long-term prospective studies of measurement of plasma/synovial sRAGE in RA subjects are needed. Is it possible that patterns of sRAGE expression might help to identify subjects in whom aggressive therapy may be indicated [13]?

These intriguing studies have striking parallels in the work of Falcone and colleagues [14]. These investigators studied non-diabetic men with or without coronary artery disease. They found that the lowest levels of plasma sRAGE in these subjects correlated with the highest incidence of coronary artery disease. These studies, as in those of Pullerits and colleagues, suggest that endogenously low levels of sRAGE might be either a biomarker of inflammation and/or part of the problem. How may this be settled? An important piece of this puzzle is solved when the cellular source(s) of sRAGE are delineated.

What are the source(s) of plasma and synovial sRAGE?

RAGE is expressed by multiple cell types, including vascular and inflammatory cells – the latter including neutrophils, mononuclear phagocytes and lymphocytes – and by synovial cells [11]. The studies reported by Pullerits and colleagues do not delineate the cellular sources of sRAGE measured in the plasma and synovial fluid. In addition, the specific mechanism by which sRAGE is generated remains unclear. Further, does the species recognized by the commercially available polyclonal and monoclonal antibodies employed by Pullerits and colleagues reflect soluble RAGE perhaps cleaved from the cell surface receptor? Alternatively, does this assay recognize novel soluble splice variants of the receptor [15-17]? The antibodies against RAGE employed in the ELISA used by Pullerits and colleagues do not distinguish between these two possible sources. Future studies must investigate precisely which sources and species of sRAGE are relevant to inflammatory arthritis.

Genetic variants, RAGE and RA

Previous studies suggested interesting links between RAGE and human arthritis [11,18]. It has previously been shown that a polymorphism of the gene encoding RAGE located within the V-type immunoglobulin domain of RAGE, which results in a glycine to serine substitution at amino acid position 82, is in linkage disequilibrium with HLA-DR4 [18]. It was therefore not surprising that the Ser82 allele was increased in RA subjects [11]; what remains to be studied is whether the variant is associated with disease activity. In that context, the V-type immunoglobulin domain of RAGE is the site of ligand binding. Thus, not surprisingly, studies in cell culture models suggested that the protein product of the Ser82 isoform displayed increased affinity for RAGE ligands versus that observed with the wild type (Gly82) form [11]. It also remains to be determined whether these variants relate to the regulation of sRAGE in plasma or synovial fluid.

Perspectives

The work of Pullerits and colleagues adds to the growing body of human data on RAGE, sRAGE, genetic variants and inflammation. These investigators placed sRAGE for the first time in synovial fluid and indicate that its levels might be modulated by intense anti-inflammatory therapy. Although 'cause or effect' may not be elucidated from these experiments, prospective studies in RA and other inflammatory disorders should be undertaken to delineate whether sRAGE levels are a reproducible and predictive biomarker for the extent of inflammatory arthritis and/or the response to disease-modifying/anti-inflammatory therapy.

Competing interests

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