Editorial

Altered fractalkine cleavage results in an organ-specific 17 kDa fractalkine fragment in salivary glands of NOD mice

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Abstract

Sjögren's syndrome is a rheumatic disease in which the salivary and lacrimal glands are the principal targets of a pathological autoimmune reaction. Previous studies in mice indicated that delayed organogenesis and aberrant cell physiology followed by an increase in acinar cell apoptosis precede chronic focal inflammation in the salivary glands and the manifestation of impaired exocrine gland secretion. In a recent study by Wildenberg and colleagues, the authors report aberrant proteolytic activity in the salivary glands of non-obese diabetic mice and the generation of a unique organ-specific 17 kDa fragment of the chemokine and adhesion molecule fractalkine.

In the previous issue of *Arthritis Research & Therapy*, aberrant proteolytic activity in the salivary glands of non-obese diabetic (NOD) mice with spontaneous experimental Sjögren's syndrome (SS) was reported [1]. SS is a rather common systemic autoimmune disease characterized by exocrine gland inflammation and impaired glandular function [2]. The NOD strain has become a commonly used spontaneous model for SS in which several SS-related hypotheses have been developed or tested. Although the initiating event leading to the accumulation of mononuclear cells in the exocrine glands is unknown, studies in NOD mice and related congenic strains carrying the *Aec1* and *Aec2* loci showed aberrant proteolytic activity [3], elevated apoptosis and activated interferon-γ, Toll-like receptor (TLR)3 and TLR7 associated pathways in the salivary glands prior to manifestation of the disease [4].

Wildenberg and colleagues [1] now provide evidence that fractalkine is cleaved to a unique organ-specific 17 kDa fragment in the salivary glands of NOD mice. This phenomenon was observed from as early as 10 weeks of age. At this time-point the mice probably displayed a pre-disease or sub-clinical stage of SS [5]. Altered cleavage was subsequently observed until 20 weeks of age when SS in NOD mice is thought to have advanced to an overt disease stage [5]. Unfortunately, the protease involved in the cleavage of this apparently unique and organ-specific17 kDa fragment has not yet been identified. The cleavage, however, did not seem to depend on Caspase-3, ADAM-10, ADAM-17, MMP-2 and/or MMP-9 activity [1]. Throughout the same period of time, NOD mice presented autoantibodies recognizing 31 kDa fractalkine.

The authors mainly discuss their finding from the perspective of fractalkine as a potentially new autoantigen in SS [1]. Although such hypotheses are highly speculative considering the present core of knowledge, we believe that chemokines in general, and fractalkine in particular, deserve more attention in SS research. We recently found specific chemokines to be associated with different aspects of experimental SS [6], and prevention of hyposalivation in NOD mice through administration of heat-shock protein 60 kDa coincided with normalization of multiple chemokine levels in saliva [7].

In contrast to other chemokines, fractalkine can be found in two specific forms, which allows fractalkine to participate in very distinct biological processes. Soluble fractalkine acts as a potent chemotactic factor for monocytes, natural killer (NK)-cells, and T-cells expressing CX3C receptor (CX3R)1. In addition, a membrane-anchored form, which is unusual for chemokines, is expressed on endothelial cells and also several cell types associated with exocrine glands [8]. To what extent fractalkine expression patterns might be altered in salivary glands obtained from patients with SS in comparison with viral infections or homeostatic conditions, however, remains to be investigated [8].

CX3R = CX3C receptor; NK = natural killer; RA = rheumatoid arthritis; SS = Sjögren's syndrome.

By acting as an adhesion molecule, membrane-bound fractalkine may facilitate extravasation of CX3CR1-expressing leukocytes [9,10]. In addition, CX3CR1 appears to be a selective surface marker for leukocyte subsets, which exert cytotoxic effector functions. Fractalkine may also lead to increased interferon-γ, tumor necrosis factor-α and granulocyte monocyte colony stimulating factor production by NK-cells and other cell subsets that have been suggested to play a role in the initiation phase and pathogenesis of inflammatory conditions, such as atherosclerosis [10], glomerulonephritis [9] and rheumatoid arthritis (RA) [9]. Although these disorders are multifactorial in nature, exposure to microbial agents is thought to play a role in their initiation [2,9,10]. Several viral proteins were reported to bind a broad spectrum of mediators of the immune system, including fractalkine [8]. Specific gene polymorphisms have been reported to be risk factors for coronary heart disease [10] and deletion of CX3CR1 in apolipoprotein E deficient mice reduced atherosclerotic lesion formation [10]. Fractalkine has also been associated with the pathogenesis of RA after fractalkine and CX3CR1 expression were reported to be upregulated in the synovium of patients with RA [9]. Supporting the notion of the disease-modulating activity of fractalkine in RA, administration of anti-fractalkine antibodies ameliorated experimental RA [9]. With regard to diseases involving the kidneys, a viral fractalkine antagonist reduced kidney inflammation and proteinurea in the Wistar-Kyoto crescentic glomerulonephritis model [9]. In concordance, anti-CX3CR1 blocked lymphocytic infiltration and the development of subsequent stages of glomerulonephritis in these rats [9]. In MRL^{lpr} mice a truncated fractalkine analogue with the capability of antagonizing the actions of fractalkine also significantly ameliorated several aspects of lupus nephritis and vasculitis [9].

The findings reported by Wildenberg and colleagues add the aspect of organ-specific cleavage of fractalkine to its potential role in a specific autoimmune condition. Unfortunately, the report does not address the effect of altered cleavage on fractalkine's biological activities, for example, chemotaxis. Based on the results presented it is therefore difficult to speculate if fractalkine, through altered cleavage, might be rendered either more potent or less efficient with regard to certain of its actions. The study by Wildenberg and colleagues provides, however, a rationale for conducting such functional studies in the future. In parallel, it would be interesting to address if the described autoantibodies might have the potential to modulate fractalkine related inflammatory processes.

Conclusion

The recent study by Wildenberg and colleagues provides insight into the role of fractalkine in an experimental model of SS, which, due to its dual role as chemoattractant and adhesion molecule, might play a crucial role in the initiation, accumulation and retention of inflammatory cells in the salivary glands. This corresponds to properties of fractalkine reported in other inflammatory diseases and rheumatic conditions. In SS, however, the role of fractalkine in the etiology and pathogenesis of the disease deserves to be studied further through direct manipulation of pathways involving fractalkine. More experimental evidence is also required to establish anti-fractalkine autoantibodies as a marker for SS or even to define a specific role for such autoantibodies in the pathogenesis of SS.

Competing interests

The authors declare that they have no competing interests.

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