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EDITORIAL

(Auto)immunity to cartilage matrix proteins – a time bomb?

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See related article by Geng *et al.*, http://arthritis-research.com/content/14/4/R191

Abstract

Geng and colleagues consolidate and detail the role of cartilage oligomeric matrix protein (COMP) as a (potential) autoantigen in experimental and human arthritis, a finding also supported by the detection of COMP fragments and anti-COMP antibodies in rheumatoid arthritis serum and/or synovial fluid and by synovial B-cell responses against COMP. The reactivity to COMP is yet another example of how, in addition to collagen II and the large aggregating proteoglycan, cartilage-specific proteins can induce arthritis and contribute to autoimmunity. Progression of cartilage damage and degradation in disease is believed to promote the autoimmune reaction to cartilage components. However, Geng and colleagues show that anti-COMP mAbs bind *in vivo* to undamaged cartilage, as previously also observed for anti-collagen II antibodies. Whether this autoimmunity also involves modifications of cartilage matrix proteins, such as citrullination, remains to be further investigated. Latent, subpathogenic (auto)immune reactions directed against cartilage matrix proteins may thus eventually contribute to the outbreak of human arthritis.

In a previous issue of *Arthritis, Research & Therapy*, Geng and collaborators from the laboratory of Rikard Holmdahl expand on the topic of cartilage oligomeric matrix protein (COMP) as an autoantigen in arthritis [1]. They convincingly show that mice immunized with mouse recombinant full-length COMP or COMP fragments produce a rapid and strong IgG response to these proteins/fragments beginning on day 14. The response continues over day 35, given that onset of COMP-induced arthritis occurs on days 36 to 38 [2] and peaks on day 50.

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The authors then generated mAbs by immunizing mice with the native form of recombinant rat COMP and by subsequent application of the classic hybridoma technique [3], of which 18 mAbs were cross-reactive with mouse COMP and were further analyzed. They next showed that some of the mAbs against COMP bound to cartilage *in vivo* following injection into neonatal mice, and could thus be found in the right place for the induction of the pathogenetic cascade. After thorough screening of the epitope specificities of the different anti-COMP antibodies (with four antigenic domains in COMP, but a preferential response to the epidermal growth factor-like domain), the authors finally showed that combinations of the mAbs were capable of inducing arthritis upon *in vivo* injection, either in combination with sub-arthritogenic doses of a mAb directed against collagen II or, strikingly, just by themselves. In the latter case, however, the arthritis was less severe.

In conjunction with previous reports from the same group [2,4], these results consolidate and detail the role of COMP as a (potential) autoantigen in experimental and human arthritis – a finding supported not only by detection of COMP fragments and anti-COMP antibodies in rheumatoid arthritis serum and/or synovial fluid, but also by synovial B-cell responses against COMP.

The reactivity to COMP is a further example, next to collagen II [5] and the large aggregating proteoglycan in cartilage [6], of how cartilage-specific proteins can induce arthritis and contribute to autoimmunity. Progression of damage to and degradation of the cartilage in disease is generally believed to promote the autoimmune reaction to cartilage components. However, Geng and colleagues' present paper shows that anti-COMP mAbs bind *in vivo* to undamaged cartilage, as previously also observed for anti-collagen II antibodies [7]. Whether this autoimmunity also involves modifications of cartilage matrix proteins, such as citrullination, remains to be further investigated.

The potential importance of autoimmunity to cartilage matrix proteins is further supported by the stunning and somewhat unexpected success of pure anti-B-cell therapy with, for example, anti-CD20 antibodies, in view of

decade-long pathogenetic hypotheses favoring T-cell dominance [8,9]. Strikingly, such immune activation and/or (auto)immunity is detectable both systemically and in the joint already before the onset of disease or early in experimental arthritis [10,11] and human arthritis [12,13], suggesting that these responses may be mounted before or in parallel to the final pathogenetic cascade. Latent, subpathogenic (auto)immune reactions directed against cartilage matrix proteins may thus be a time bomb eventually contributing to the outbreak of human arthritis.

In summary, the data from Geng and colleagues provide further evidence and detailed antibody specificity information about the contribution of COMP to arthritis. They prepare the ground for future studies not only relevant to rheumatoid arthritis but also to other autoimmune diseases, given that some of the mAbs are not only cross-reactive between mouse and rat but also with human. We are looking forward to seeing the future fruits of this favorable research.

Abbreviations

COMP, cartilage oligomeric matrix protein; mAb, monoclonal antibody.

Competing interests

The authors declare that they have no competing interests.

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