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Autoimmunity to a ubiquitous glycoprotein targets the synovial joint

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Keywords

Arthritis, autoimmunity, autoantibody, autoantigen, glycolytic enzyme

Context

There is no compelling evidence either for or against the notion that chronic arthritis is driven by an autoimmune response to cartilage specific antigens. Accordingly, the identification of self antigens implicated in the development of spontaneous arthritis would be an important advance. In 1996, the Mathis and Benoist laboratory reported a spontaneous mouse model of arthritis in a T cell receptor (TCR) transgenic line, with features resembling rheumatoid arthritis (RA) in man (Kouskoff *et al* 1996, *Cell* **87:** 811. Earlier this year the same group reported a series of elegant experiments which demonstrated distinct roles for T and B lymphocytes in the progression to disease, where T cells were critical during the early phase, despite evidence of multiple levels of tolerance, and B cells were important for the effector phase (Korganow *et al* 1999, *Immunity* **10:** 451 [Paper report]). Importantly they demonstrated that arthritis could be transferred using a single intravenous injection of serum from arthritic mice. All the results pointed to a model in which transgenic T cells recognise a ubiquitous self antigen presented by non-obese diabetic (NOD) mouse MHC class II molecules in the periphery, and that sustained, systemic immune activation targeted synovial joints through processes involving activation of B cells and the production of high affinity arthritogenic autoantibodies. Identification of the specific autoantigen(s) responsible for the disease process was a priority. To identify the autoantigen(s) responsible for driving systemic autoimmunity in a spontaneous mouse model of rheumatoid arthritis.

Significant findings

Western blotting using serum from arthritic but not healthy mice identified an approximately 60 kDa protein in extracts of ankle, kidney and spleen. Purified IgG identified a similar band which was subsequently found by sequencing of tryptic peptide fragments to be glucose-6-phosphate isomerase (GPI), a glycoprotein of known molecular weight (62.6 kDa). By ELISA it was possible to demonstrate immunoreactivity in sera from arthritic mice to recombinant GST-GPI from as early as 3 weeks (around the time of arthritis onset), peaking at 8-10 weeks of age. Titres varied from 1:100 to 1:1,000,000. Significantly, immunoglobulin eluted from GST-GPI coupled matrices could transfer arthritis to recombination activating gene (RAG) deficient recipients following a single injection, with features

typical of those observed in the original KRN TCR transgenic K/B x N mouse arthritis model. This confirmed that the target antigen was GPI, and that anti-GPI specific antibodies alone were arthritogenic in mice. NOD mouse antigen presenting cells (APCs) pulsed with GPI were capable of stimulating the original T cell hybridoma used to generate the KRN transgenic line, as well as resting TCR transegic T cells. Responses were comparable to those obtained following stimulation of the same T cells with bovine ribonuclease peptide 41-61 (the original specificity of KRN T cells) and I-Ak expressing APCs.

Comments

This report demonstrates for the first time that chronic activation of peripheral lymphocytes by ubiquitous antigen leads to an autoimmune response that selectively targets synovial joints. The data challenge the long held but unproven notion that the pathogenic process is driven by activation of the immune system by tissue specific (cartilage) antigens, a paradigm based almost exclusively on the collagen-induced arthritis model in rodents. Now that the antigen is known, the model can be exploited to pin down precisely the role of immunoglobulin, immune complexes and FcR in the effector stage of the disease process. The role of GPI or antigens with similar physicochemical properties can also be explored in different subsets of patients with chronic inflammatory arthritis. It may turn out that unique anatomical characteristics of the synovial joint may play some additional, previously unrecognised role. Is it possible that in 10-20 years time, this report will be cited as one of the more significant archive papers to have contributed to our understanding of the pathogenesis of chronic inflammatory arthritis in the "old millenium"?

Methods

Sera from arthritic K/B x N or healthy control mice were used as "probes" for blotting and immunoprecipitation experiments using mouse tissue extracts as a source of putative autoantigen. Purified IgG fractions from sera of arthritic mice were used to affinity purify antigen, and to confirm the identity of the candidate autoantigen. Specific bands identified by blotting with these sera were excised prior to trypsin digestion, HPLC purification of peptide fragments and sequencing by Edman degradation. Recombinant fusion proteins of glutathione S-transferase (GST) coupled to autoantigen expressed in *E. coli* were used in blotting and ELISA experiments, and as a source of pure antigen to affinity purify immunoglobulin from sera of arthritic mice for use in arthritis induction experiments.

References

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