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BiP - a new autoantigen

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Keywords

Activated T cells, animal models, immunotherapy, RA

Context

Autoimmune processes in rheumatoid arthritis (RA) remain poorly understood. Various autoantigens have been defined, though their role in initiation of RA remains unclear. This study sought to identify autoantigens directly by cloning genes encoding joint proteins reactive with patients' antisera, and to characterize T-cell responses to homologous proteins in animal models of arthritis. BiP, an autoantigen newly identified using this strategy, is a chaperone protein involved in folding of many proteins, including immunoglobulins, in the endoplasmic reticulum.

Significant findings

Sera from 30% of 54 RA patients reacted with a 70-kDa protein on western blots; 10% of 11 patients with other (RF-negative) arthritides reacted. This reactivity could be removed by adding recombinant human BiP. Synovial fluid T cells from 50% of 23 RA patients, versus 20% of disease controls, proliferated in response to recombinant human BiP; peripheral blood T cells proliferated less. Responsiveness to BiP did not associate with HLA-DR4, but anti-DR monoclonal antibodies partially blocked the response. BiP was not arthritogenic in susceptible mouse strains, but autoAbs to BiP developed in animals with collagen- or pristane-induced arthritis. Injection of BiP intravenously before collagen immunization diminished incidence and severity of collagen-induced arthritis, and IgG subclasses shifted, suggesting immune deviation towards a Th2 phenotype. Adjuvant arthritis in rats was also ameliorated by recombinant human BiP. The authors concluded that BiP is a novel RA autoantigen and proposed that manipulation of responses to BiP may ameliorate RA.

Comments

This work adds to a growing list of autoantigens implicated in human RA and its animal models. The statistical significance of RA association with anti-BiP antibody responses was not reported, and data showing antibody specificity were weak. Given the apparent inability of BiP to initiate arthritis in animals, an involvement in determinant spreading seems more likely than a role in initiation. BiP, like several other putative RA autoantigens (hsp70, HCgp39, glucose 6-phosphate isomerase), is expressed systemically, so these results raise the important question of how a systemic autoantigen causes a disease whose manifestations are largely (though not completely) localized to joints. The possibility of using BiP in immunotherapy of human RA is intriguing, but an important caveat is that BiP was not shown to reverse established arthritis. Could the pathogenic mechanism involve the natural ability of BiP to bind immunoglobulin heavy chains?

Methods

western blot, collagen-, pristane- and adjuvant-induced arthritis, T-cell proliferation, histology

Additional information

References

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