HYPOTHESIS

Ankylosing spondylitis, IgA, and transforming growth factors

J R Archer

This hypothesis article reviews laboratory findings in seronegative arthritides with a view to discovering which cytokines are likely to be most important in their pathogenesis. It concludes that transforming growth factors may play a significant role, and suggests that they derive from a group of T cells which have recently been rather neglected by academic immunologists.

Ankylosing spondylitis (AS) and psoriasis are unusual in being primarily associated with class I HLA molecules—AS with B27, psoriasis usually with Cw6—so that many of their epidemiological properties seem to be either identical or complementary. Many of the B27 negative patients with AS also suffer from psoriasis, while psoriasis patients who are B27 positive tend to develop an axial arthritis. Rats carrying the transgenic human B27 gene develop both psoriasis and arthritis. This last observation may be connected with the fact that normal rats differ from humans in having only one locus equivalent to the human HLA-A, -B, and -C, so that any subtypes relating to differences in biological properties between HLA-B and -C antigens are likely to be lost in these animals. AS and psoriasis are both also associated with high levels of serum IgA. As it seems unlikely that this is a coincidence, this article considers possible reasons for a connection between serum IgA and class I susceptibility in the case of AS.

The original observation that AS is associated with high levels of serum IgA has been confirmed frequently. However, as several AS patients have been described who were IgA deficient, IgA is clearly not an essential element in the disease pathology. The interest is in its ability to act as a marker for an underlying process.

Although most observers have shown some positive correlation of serum IgA with disease activity, it has been suggested that their conclusions are disproportionately influenced by inclusion of data from patients with peripheral symptoms. In studies from which such patients were excluded, it was not possible to show a correlation between baseline IgA and inflammation of the axial skeleton, although longitudinal studies demonstrated a correlation between serum IgA and changes in severity of arthritis in individual patients. In one of these studies, in which serum IgA concentrations were compared with a radiological assessment of the lower back and pelvis, high IgA was always associated with severe radiological damage. Because IgA is the main immunoglobulin in secretions from mucosal tissues, high levels of IgA have frequently been interpreted as evidence for mucosal infections. This neglects the fact that potentially IgA producing cells can also be found in AS patients' blood and, more significantly, in their peripheral joints. Two subtypes of IgA are recognised in humans: although in normal individuals most secretory IgA is IgA2, both of the laboratories which have measured subtypes in AS patients found that a substantial proportion of circulating antibody was IgA1. Some controversy remains over whether these results can be interpreted as showing evidence for mucosal stimulation, but it is clear that antibody synthesis occurs independently of the mucosa and the initial stimulus for its production may also be non-mucosal.

Recent developments have helped to define the controls deciding the immunoglobulin isotype which a B cell produces. Stimulation of B cells by antigen in the presence of appropriate CD4 positive helper T cell stimuli causes maturation of the antibody response. Part of this involves a rearrangement of the immunoglobulin genes to bring the heavy chain V, J and D genes, which define antibody specificity, into close proximity to the C-genes which define isotype. The precise C gene to be activated is determined by the availability of particular cytokines at the time of rearrangement. So, by identifying the isotypes of circulating heavy chains, it may be possible to identify which cytokines were present when their genes were first activated. In the case of IgA in humans, these cytokines have consistently been reported to be transforming growth factor β (TGFβ). Interleukin (IL)-5 has also been shown to enhance IgA production by human B cells—a process which is specifically inhibited by IL-4. Several murine studies suggest that IL-5 acts subsequently to TGFβ on clones which are already committed to IgA production. It is likely, therefore, that in diseases characterised by high serum IgA, including AS and psoriasis, part of the mechanism of their pathogenesis includes production and activation of TGFβ or a closely related molecule, and possible also that IL-5 is involved.

TGFβs are an important family of molecules in the formation and repair of cartilage and bone, in which concentrations can be 100 times greater than are found in other tissues. This has been reviewed elsewhere. Extra amounts are produced by cells from the
perioseal sheath during the repair of rat tibial lesions—a process during which production of TGFβ correlates initially with early intra- membranous bone formation, and subsequently with chondrogenesis immediately preceding endochondral ossification. Injection of TGFβ into the perioseal sheath of young rat bone causes formation of a cartilaginous mass which converts to bone as soon as the injections cease. TGFβ is therefore a good candidate for a key cytokine in a disease in which ankylosis of the sacroiliac joints is a major symptom. However, inert TGFβ can be produced by almost any cell after suitable stimuli, and subsequently require activation. Hence, we need a mechanism by which they might be delivered specifically. Can any of these potential sources be associated with the histocompatibility antigens of AS?

The function of B27 and other HLA class I molecules is to assist in the interaction of cells with CD8 positive T lymphocytes. Older textbooks divide these into cytotoxic (Tc) and suppressor (Ts) cells, but Ts cells have recently been unfashionable, perhaps because they are more difficult to manipulate experimentally. Mouse and rat studies suggest a connection between TGFs and these Ts cells. Normally, TGFs are thought of as inhibitors of the immune response. For example, they temporarily block the activity of Tc cells. However, in activated CD8 positive cells they can specifically stimulate mitosis. Several studies on CD8 positive Ts cell clones suggest that they make TGFβ mRNA, although stimuli have not been found which will persuade these cells to synthesise the protein. However, in a study of experimental allergic encephalitis in the rat, antigenic stimulation of a mixed population of rat Ts cells with myogenic basic protein caused secretion of TGFβ.

Cytotoxic CD8 positive cells reactive with B27 positive cells have already been identified in patients with reactive arthritis and AS. Mouse models, partly confirmed in humans, suggest that these cells are capable of producing a mixture of cytokines, particularly interferon gamma, which would cause an inflammatory response. However, the information summarised here indicates that the most important CD8 positive cells in AS may belong to a suppressor subgroup which are activated as the inflammation is reduced. Two possible connections are suggested. Either a stimulus which 'activates' the HLA-B27 positive cell also leads to production of TGFβ, or many of the features of AS are byproducts of activation of CD8 positive suppressor cells.

In summary (figure), this article suggests that data on IgA production in patients can be interpreted as showing that TGFβs are significant in the pathology of AS and psoriasis. Whether they have a role in the initial inflammatory reactions is not clear; but they are likely to be important in the repair processes which lead to bone formation at Romanus lesions. It is speculated that the source of these TGFs is a stimulated CD8 positive Ts cell, reacting with HLA-B27 which has been 'activated' by an unknown mechanism.


Ankylosing spondylitis, IgA, and transforming growth factors.

J R Archer

Ann Rheum Dis 1995 54: 544-546
doi: 10.1136/ard.54.7.544