Infection in the aetiology of spondyloarthropathies

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The diseases which make up the spondyloarthropathies (Table 1) appear dissimilar, with little in common between, for instance, a self-limiting monoarticular attack of reactive arthritis (ReA) and the progressive spinal deformity of ankylosing spondylitis (AS). The justification for grouping them together rests on:

- clinical observations
- genetic associations
- evidence of common pathogenic mechanisms.

Infection is involved at each of these points. Clinical observations implicate bacterial infection in ReA. The principal gene associated with spondyloarthropathy is HLA-B27, and infection is the driving force behind HLA polymorphism. Observations in ReA and animal models suggest a central role for bacteria in pathogenic mechanisms. This article reviews current understanding of spondyloarthropathy, the involvement of infectious agents, and the clinical implications of these ideas.

Table 1. Principal forms of spondyloarthropathy.

- Reactive arthritis
- Arthritis associated with inflammatory bowel disease
- Psoriatic arthritis
- Undifferentiated spondyloarthropathy
- Ankylosing spondylitis

Common features of the spondyloarthropathies

Clinical features

Several clinical features distinguish the spondyloarthropathies from rheumatoid arthritis, including their targeting the axial skeleton and sacroiliac joints, preferential involvement of large joints, and asymmetry. There are also common extra-articular features, particularly enthesopathy (tendon inflammation at insertion into bone), and involvement of other tissues such as skin and eyes. Table 2 lists the clinical features and their approximate frequency in different forms of spondyloarthropathy, but any feature can be found in any form and patients may be classified differently at different times. Examples would be ReA evolving into AS, or a patient with psoriatic arthritis (PsA) suffering an episode of enteric ReA. Taken together, these clinical observations suggest a core set of articular and extra-articular features which define the spondyloarthropathies. These are reflected in classification systems, for example the ESSG criteria (Table 3).

Genetics

Genetics in spondyloarthropathy has been dominated by the association between AS and HLA B27, but B27

Table 2. Clinical features of spondyloarthropathies.

	Reactive arthritis	Psoriatic arthritis	IBD-associated arthritis	Ankylosing spondylitis
Joint involvement				
Spine	+	+++	++	++++
Sacroiliac	+	+++	++	++++
Peripheral joints:				
large	+++	++	+++	+++
small	++	+++	++	+
Dactylitis	++	+++	+	+
Extra-articular features				
Eyes	Uveitis Conjunctivitis	Uveitis	Uveitis	Uveitis
Skin	Keratoderma Balanitis Erythema nodosum	(Psoriasis)	Erythema nodosum	
Heart	Aortitis		Aortitis	
Bowel	(Enteritis)		(IBD)	Subclinical IBD

The number of + signs gives the approximate frequency of the feature in different forms of spondyloarthropathy (++++ = invariable; +++ = common; ++ = well recognised; + = recorded).
μIBD = inflammatory bowel disease.

is also associated with other forms of spondyloarthropathy:

- axial disease in PsA, or the arthritis of inflammatory bowel disease (IBD)
- ReA with severity and persistence.

The effect of B27 is strongly dependent upon other genes and environmental factors. In AS, the interaction of B27 with other genes is shown by the tenfold greater risk of developing the disease in B27-positive offspring of AS patients. Thus, in classical AS, B27 is necessary but not sufficient, whereas in AS complicating psoriasis, B27 is not absolutely necessary (only 50% of patients are positive), and an additional set of genes and/or environmental influences determine outcome. Likewise, anyone can develop ReA (the incidence of B27 varies in different series), but B27 increases the likelihood and produces a more severe phenotype. Recent studies implicate other genes mapping to the MHC acting in association with B27[1].

Pathogenic mechanisms

A complete description of pathogenesis is not yet available for any form of spondyloarthropathy. ReA has proved the most tractable to investigation, because of its acute onset and triggering by known infectious agents. A current view of its pathogenesis is summarised in Figure 1. First, although triggering bacteria cannot be cultured from affected joints, there is abundant evidence that bacteria reach the joint. Bacterial antigens (proteins and lipopolysaccharides) can be detected[2], as can DNA. Recent observations detecting bacterial RNA in chlamydia- and yersinia-induced ReA[3,4] strongly suggest that the bacteria are viable in the joint, even though they seem incapable of replicating – bacterial RNA is very unstable compared to DNA, and does not persist after the death of the organism. Secondly, activated T lymphocytes responding to triggering organisms are readily detected in affected joints. Most information is available on CD4+ T cells, and the precise role of CD8+ T cells reactive to bacterial antigens in the context of B27 remains unclear.

Table 3. Eurpoean Spondylarthropathy Study Group (ESSG) criteria for spondyloarthropathy.

Inflammatory spinal pain

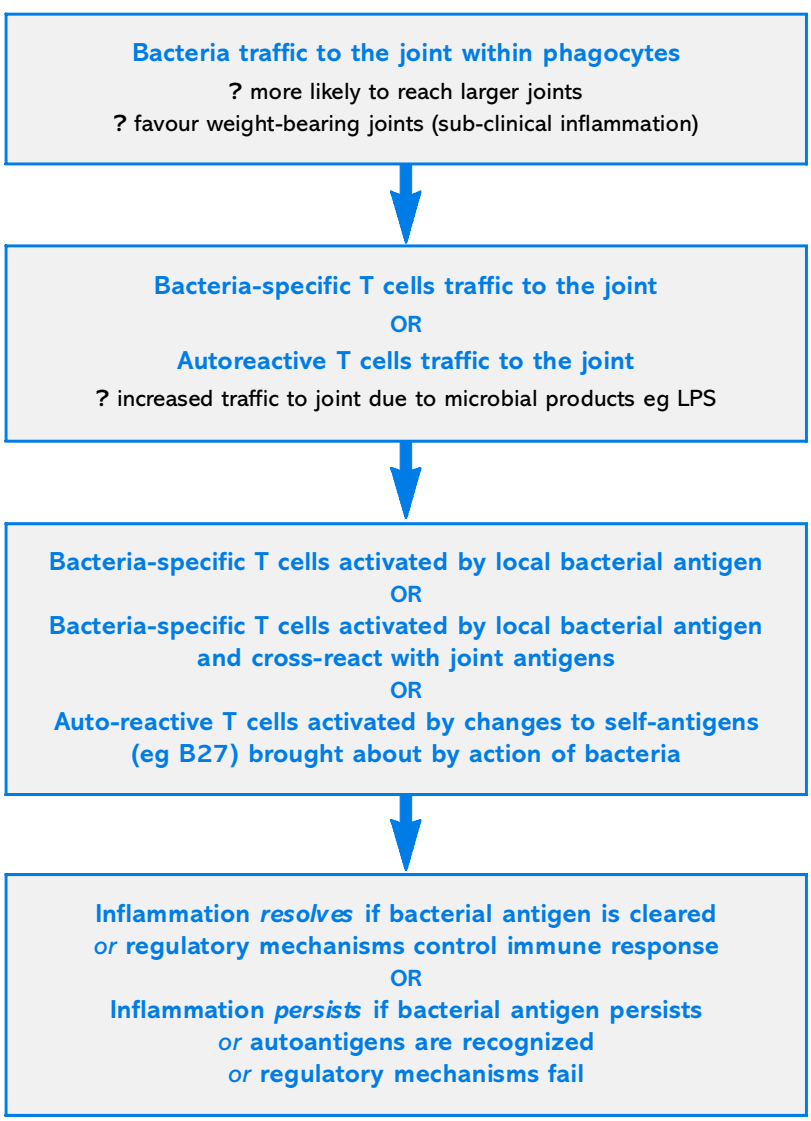
or

asymmetric/predominantly lower limb synovitis

plus one or more of:

- Family history
- Psoriasis (past or present)
- Inflammatory bowel disease : (past or present)
- Urethritis or cervicitis (within 1 month of diagnosis)
- Acute diarrhoea (within 1 month of diagnosis)
- Enthesopathy (past or present)
- Sacroiliitis on radiographs (bilateral Grade 2–4 or unilateral Grade 3–4)

Fig 1. Pathogenesis of reactive arthritis



Although bacterial antigens can be detected, they are not abundant and demonstration of bacterial DNA and RNA requires polymerase chain reaction techniques. In addition, RNA from triggering organisms may be only a minor component of the total bacterial RNA which may reach the joint: for example, RNA from commensal bacteria which traffic to the joints within phagocytes but do not survive there.

Similarly, only a proportion of T lymphocytes in an ReA joint recognise the triggering organism. An inflamed joint recruits circulating memory T lymphocytes non-specifically, so T cells reactive with many recall antigens reach the joint. The question is to what extent do local bacterial antigens stimulate antigen-specific T cells in the joint, and is this critical to joint inflammation? Alternatively, activation of organism-specific T cells which reach the joint does not depend on a small amount of local antigen but takes place elsewhere, or the T cells cross-react with some self-antigen in the joint. B27 itself might be such a target, but as yet there is no direct evidence for this hypothesis.

Involvement of bacteria in ReA is clear. It is less so in other forms of spondyloarthropathy. In PsA and arthritis associated with IBD, inflammation occurs at a major interface with the commensal bacteria of the gut and skin. Compromise of the interface might constitute an 'infectious trigger' in the same way as infection with an invasive organism in ReA. Direct evidence is lacking, however. The most compelling evidence for involvement of infectious agents in forms of spondyloarthropathy other than ReA comes from studies in HLA B27 transgenic rodents. Both rats and mice develop spontaneous arthritis. In rats, clinical features of spondyloarthropathy, including IBD, are recapitulated to a surprising extent[5]. In both cases, disease requires bacteria within the gut (ie germ-free animals remain arthritis-free). Experiments infecting germ-free B27 transgenic rats with particular bacteria suggest that anaerobic organisms are sufficient to allow disease. These observations in experimental animals, coupled with reports of subclinical IBD in a proportion of patients with classical AS, suggest a role for gut-derived organisms in AS[6]. *Klebsiella pneumoniae* has attracted attention in AS, based principally on raised titres of antibody to klebsiella in AS. It is less clear whether AS patients carry more klebsiella in the gut than control subjects. Although it is possible to find examples of conserved sequences in klebsiella antigens and joint components, and to show that antibodies reactive with klebsiella cross-react with these, such examples of molecular mimicry may not play any role in disease. Increased antibodies to klebsiella may reflect subclinical bowel disease and increased exposure of the immune system to the organism.

A current view of spondyloarthropathies suggests that they are related to a failure to deal appropriately with bacterial challenges, whether by pathogens or commensals. HLA-B27 would be one gene contributing to this failure, but others might substitute or have similar effects. It is unclear what makes the response to bacterial challenge inappropriate. Hyperresponsiveness to particular bacterial antigens could produce tissue damage. Alternatively, an inadequate response to bacteria might delay their clearance from sites such as the joint to which they might normally traffic. It is clear that the immune system treats normal gut flora (appropriately) as self. Some disturbance of this relative tolerance of gut bacteria may underlie both IBD and spondyloarthropathy.

Key Points

- Spondyloarthropathies have common clinical features
- Common pathogenic mechanisms are likely
- Specific pathogens trigger reactive arthritis (ReA)
- Commensal bacteria may be involved in other forms of spondyloarthropathy
- Bacteria and bacteria-specific T cells are present in the joint in ReA
- B27 affects severity and persistence in spondyloarthropathy
- Antibiotics have not been shown to be effective

Practical considerations

What are the practical implications of the current view of the pathogenesis of the spondyloarthropathies? In the interest of accurate diagnosis, it is worth considering ReA in any individual developing an otherwise unexplained inflammatory oligoarthritis. The triggering infection may be virtually asymptomatic, but appropriate history, culture and serology may indicate the correct diagnosis and allow a more accurate prognosis. Occult IBD and psoriasis (or psoriasis which has not yet presented) should be borne in mind in patients who have features of the spondyloarthropathies. Patients with unclassified spondyloarthropathy are not uncommon and a proportion will evolve into one of the more recognised spondyloarthropathies. The prevalence of spondyloarthropathy *in toto* is not very different from that of rheumatoid arthritis, so it is important to classify this group as accurately as possible in order to define their management. There are already reports of good responses to anti-tumour necrosis factor therapies in spondyloarthropathy[7,8] but, in view of the implication of infectious agents in pathogenesis, it will be important to follow this treated group carefully to determine whether there are late sequelae.

The final question concerns treatment with antibiotics. There is no definitive answer about the value of antibiotics in ReA, but the weight of trial evidence is against it[9,10]. Unfortunately, antibiotics, as currently used, may not be able to eliminate the organisms which traffic to

the joint and are in a non-culturable state, so the lack of efficacy of antibiotics does not in itself refute the idea that bacteria are central to the pathogenesis of ReA or other spondyloarthropathies.

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Tumour necrosis factor blockade in rheumatoid arthritis

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Rheumatoid arthritis (RA) is one of a group of conditions frequently referred to as autoimmune diseases. Joint pain and joint immobility, which are characteristic of RA, arise from a chronic fluctuating inflammation in the synovial tissue of the joints. Although the mechanism by which this immune-mediated inflammation is triggered and the nature of the target antigen remain to be elucidated, mediators that perpetuate inflammation and destruction of cartilage and bone have been identified. On the basis of this increasing knowledge, new therapeutic principles have been developed with biological agents that act on more specific targets than the established antirheumatic drugs.

The possible targets for intervention that have recently received most attention are cytokines[1]. Cytokines can be categorised as those that enhance inflammation, such as tumour necrosis factor (TNF) or interleukin (IL)-1, and those that decrease inflammation, such as IL-10 or IL-4. Several natural endogenous inhibitors of TNF and IL-1 have been identified, including IL-1 receptor antagonist, soluble IL-1 receptors, and soluble TNF receptors. These natural inhibitors are present in healthy persons, with higher levels in RA patients in serum and at sites of inflammation. In RA, pro-inflammatory cytokines outnumber anti-inflammatory cytokines or natural inhibitors[2]. This has stimulated the search for agents that can restore this imbalance.

Tumour necrosis factor

TNF is a pleiotropic cytokine abundantly produced in the rheumatoid synovium. It binds to the surface receptors of cells, leading to a pattern of gene activation. This process causes:

- macrophages to produce pro-inflammatory mediators that amplify the inflammatory reaction
- endothelial cells to express adhesion molecules that allow access of more inflammatory cells to the site of inflammation
- fibroblasts to produce proteases that can destroy cartilage, bone and ligaments[2].

The spontaneous development of destructive arthritis in mice transgenic for TNF[3] can be prevented by the administration of TNF monoclonal antibodies (mAb) that bind and inactivate TNF. TNF given intra-articularly induces synovitis; if administered during the development of collagen-induced arthritis it leads to a more severe form of joint inflammation. However, mice receiving TNF mAb at the same time show significant amelioration of the disease process[4]. TNF may also contribute to systemic features of RA by stimulating acute-phase protein synthesis and inhibiting erythropoiesis[5].

Clinical trials

Tumour necrosis factor antibody

In the first half of the1990s, clinical trials using chimeric human/mouse or humanised TNF mAb in RA patients provided the first direct evidence that

Key Points

Tumour necrosis factor (TNF) plays a pivotal role in chronic inflammation

TNF blockade in rheumatoid arthritis decreases inflammation and joint destruction, and maintains function