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Review

The critical role of interleukin-23 in spondyloarthropathy☆

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ABSTRACT

The spondyloarthropathies represent highly enigmatic conditions and although their clinical features, anatomical distribution of disease and genetic predisposing factors have been known for some time, a unified concept of the basic pathobiology underlying these illnesses has remained undefined. Recently progress has been made because numerous independent studies have converged upon IL-23 as a central cytokine in spondyloarthropathy and the mechanism and sites of action of this cytokine have now become much clearer. These findings enable the rational design of therapeutic strategies which it is hoped will profoundly modify the progression of these diseases. We will review the anatomical sites affected and the evidence for the importance of IL-23 in these conditions, before drawing these lines of investigation together to propose a model for the unified understanding of spondyloarthropathy.

1. Introduction

Systemic rheumatic diseases result from multiple aetiological factors with complex genetic and environmental components. These illnesses frequently display a broad anatomical distribution of pathology with a wide range of organ involvement, yet each disease has a typical set of involved organs. Indeed each affected organ displays characteristic pathologies in subanatomical regions. Despite the diversity of organ and anatomical sites affected, a common, unifying factor is frequently suspected to be at the heart of the disease process. To discover such a factor would be to locate the critical therapeutic target for such a set of diseases. Recent years have seen remarkable advances in the spondyloarthropathies in which the powerful pro-inflammatory cytokine interleukin (IL)-23 has emerged as a key pathogenic factor which not only ties together numerous observations in genetics but which also explains the specific organs and particular anatomical sites affected.

2. Anatomical distribution of disease in spondyloarthropathy

The spondyloarthropathies form a heterogeneous group which includes ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease associated arthritis, and the 'reactive' arthritis which follows a very specific set of infectious diseases (Rudwaleit et al., 2011). The axial skeleton is a dominant site of pathology in these conditions, with inflammation of the ligamentous attachments in the affected spine which results in pain, stiffness and poor mobility. In contrast to other articular diseases such as rheumatoid arthritis where inflammation is accompanied by bony erosion and destruction (Karmakar et al., 2010), spondyloarthropathy is not only characterised by such destruction, but by new bone formation (Lories et al., 2009). This new bone appears as syndesmophytes, bony outgrowths from spinal vertebrae, which when they meet can form a complete arc across the vertebrae accounting for the ultimate morbidity of such diseases: spinal fusion, with extremely detrimental effects on mobility (van Echteld et al., 2006).

The spondyloarthropathies are puzzling not simply because of their dual effects on bone, with both bone erosion and new bone formation, but also because they manifest a diverse range of systemic signs and symptoms affecting physically remote anatomical structures. The most commonly associated manifestations include aortic valve inflammation, psoriasis, and bowel inflammation. Uveitis also accounts for significant morbidity in ankylosing spondylitis. Even when not overtly manifest, the associated conditions may be present sub-clinically – for example, microscopically evident bowel inflammation is observed in almost 70% of patients with spondyloarthropathy (Mielants et al., 1995). These observations suggest that there is a fundamental unity underlying the pathology of spondyloarthropathy, yet the causal connections underlying this diversity of pathology have remained poorly understood. In particular the cells driving pathology within the canonical sites of disease remain elusive, something which hinders the design of rational therapeutics.

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3. Entheseal anatomy

A particularly intriguing feature of spondyloarthropathy is the nucleation of articular pathology to specific subanatomical regions of joints. On the basis of histological examination of the location of pathology in postmortem tissue and a number of biopsy samples, Ball proposed that the primary structure affected in spondyloarthropathy is the *enthesis*, the anatomical region where tendons and ligaments connect to bone (Ball, 1971). The pathology of these diseases thus contrasts sharply with rheumatoid arthritis where joint pathology involves the synovium as its primary target (Scott et al., 2010). McGonagle et al. (1998a) have proposed that enthesitis is so fundamental to the pathology of spondyloarthropathy that a classification of arthritis can be based on the presence of enthesitis and thus the enthesis is seen to represent the anatomical structure in which the pathobiology of spondyloarthropathy must be studied. Nevertheless, the reason why disease localises to entheses in spondyloarthropathy has been enigmatic, and in particular the reason why the known predisposing genetic variants in the immune system, such as the presence of HLA-B27 or polymorphisms in IL-23R (which we will discuss later), should predispose to inflammatory pathology specifically at these very precise anatomical sites is even more puzzling. Although one longstanding hypothesis proposes that a key aspect of the enthesis which could form a basis for disease localisation to this site is the extreme physical stress to which this structure is exposed, this leaves the immunological reasons for disease localisation unclear.

It is important to emphasise that although the enthesis has been demonstrated to be the primary site of disease in spondyloarthropathy, other musculoskeletal tissues are also clearly affected including synovium, bursae and fascia. Investigators have therefore cautioned against attributing pathology exclusively to enthesitis, drawing attention to the importance of synovitis in sacroiliac joint pathology (Muche et al., 2003; François et al., 2000). In order to account for the range of pathology seen in spondyloarthropathy, McGonagle et al. (1998a) have suggested an important model in which enthesitis is proposed to be the primary event, whilst synovitis is a secondary manifestation. The most central question raised by such a model is the degree to which entheses and synovium are dependent on each other for the initiation of inflammation, and more specifically whether entheseal pathology in turn depends on immune events initiated in the synovium. Clarification of this is essential to understand how inflammation driven by IL-23 can contribute to spondyloarthropathy. We hypothesised that the enthesis is a primary site of immunological activity (Cua and Sherlock, 2011) distinct from the synovium since this would explain why the synovitis of rheumatoid arthritis does not cause enthesitis, and why the dysregulations in IL-23 associated with spondyloarthropathy result in diseases characterised by enthesopathy. Our work has therefore focussed specifically on the characterisation of the immune cells in the enthesis and the examination of their responsiveness to inflammatory mediators such as IL-23.

The model of an extended 'enthesis organ' is extremely useful in explaining the range of musculoskeletal pathology in spondyloarthropathy since it draws attention to the close relations of entheses, bone, synovium and fascia. Benjamin and McGonagle (2007) have emphasised that entheseal juxtaposition to synovium is frequent, with over four fifths of entheses being part of a 'synovial entheseal complex' and, consistent with this close physical proximity, it has been observed that synovitis in spondyloarthropathy, but not rheumatoid arthritis, is accompanied by a prominent enthesitis (McGonagle et al., 1998b). Many of the entheseal associated synovial tissues are part of bursae or tendon sheaths, rather than articular joints. Remarkably, the retrocalcaneal bursae is lined by both synovium and fibrocartilage (Canoso, 1998), demonstrating the close relationship of entheseal associated tissue and synovium in one anatomic structure, particularly one in which inflammation often accompanies Achilles enthesitis.

In addition to their close relation to synovial surfaces, many tendons have complex attachments to connective tissue. Thus rather than inserting to bone *via* a simple enthesis, tendons often have indirect insertions to bony tissue *via* attachments to extensive fascial planes. Such a distribution of mechanical connectivity is particularly prominent in the lower limbs (Benjamin et al., 2008) and around the sacroiliac region, the sites of pathology in spondyloarthropathy. Such interconnections between entheses, fascia and periosteum may explain the distribution of inflammation within these tissues which is characteristic of spondyloarthropathy, including the periostitis frequently seen in psoriatic arthritis in particular. The similarity of entheses and periosteum has also been emphasised, particularly in view of the anatomical role of periosteum as an insertional site, and its ability to form fibrocartilage following compression (Benjamin and McGonagle, 2001). The most obvious additional entheseal anatomical relationship is with the bone to which the tendon inserts. This relationship has been proposed to explain the bone oedema seen in spondyloarthropathy since in a study of the knee this was observed to be maximal at the site of entheseal attachment and accompanied by perientheseal oedema (McGonagle et al., 1998b).

Although histopathological studies have long supported the primary role of the enthesis in spondyloarthropathy, a large series of recent imaging studies have confirmed that entheseal inflammation is indeed a central feature of pathology. Thus in contrast to the intracapsular synovial inflammation seen in the knee in rheumatoid arthritis, the inflammation associated with spondyloarthropathy involves extra-capsular regions (Jevtic et al., 1995). Both magnetic resonance imaging (Emad et al., 2010, 2009) and ultrasonography (de Miguel et al., 2009; Alcalde et al., 2007; Borman et al., 2006; D'Agostino et al., 2003; Lehtinen et al., 1994) demonstrate that in contrast to the synovitis of rheumatoid arthritis, subclinical rheumatic disease in spondyloarthropathy is characterised by enthesitis. Thus the enthesis appears as an 'epicentre' from which inflammation spreads to neighbouring structures (Tan et al., 2007).

Whilst the considerable body of work described above has characterised in great detail the anatomy of entheses and related this to their clinical involvement in the spondyloarthropathies, much less is known about the immunological cell biology of enthesitis. Whilst clinical specimens are highly limited, in one study of patients entheseal biopsies were obtained from clinically involved peripheral sites. Immunohistochemical analysis of these specimens demonstrates the presence of macrophages and neovascularisation in these early lesions, in the absence of detectable CD3+ or CD8+ lymphocytes (McGonagle et al., 2002). Bollow et al. (2000) have similarly demonstrated the presence of macrophages in early sacroiliitis, accompanied by T lymphocytes. Unfortunately, CD4 staining in formalin fixed sections has often been impossible for technical reasons. Other studies have assessed related rheumatic tissues, often in patients with longstanding or very severe clinical disease. In patients with complete spinal ankylosis, spinal bone marrow examination has demonstrated aggregates of T cells including marrow CD4+ and CD8+ T cells (Appel et al., 2006a, 2006b). Synovial pathology also reveals the presence of CD4+, CD3+ and CD8+ T cells in spondyloarthropathy patients (Baeten et al., 2001; Kidd et al., 1989).

These considerations reveal that a great deal of information exists on the specific anatomical sites involved in spondyloarthropathy however the underlying reason for this tissue localisation has been unclear. In particular although the cell biology of the synovium is reasonably well known, specific information on *entheseal* resident cells has remained limited. In order to