Recent advances in spondyloarthritis: positive developments in the seronegative domain

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There have been significant developments in the field of inflammatory joint diseases in recent years. Improved clinical classification and nomenclature have brought some clarity to clinical research in this field. Older terminology divided such joint diseases into seropositive arthritis (rheumatoid arthritis) and seronegative arthritis (spondyloarthropathies) by the presence or absence of rheumatoid factor. By general consensus, the latter group is now referred to as spondyloarthritis (SpA), of which there are two major subsets: axial SpA (predominantly ankylosing spondylitis) and peripheral SpA (predominantly psoriatic arthritis).

Other controversies in terminology reflect the changing concepts in pathogenesis, in particular whether SpA should be considered fundamentally an autoimmune process or an autoinflammatory one. With few exceptions, SpA does not have a distinctive autoantibody signature which characterizes autoimmune diseases such as rheumatoid arthritis or lupus. On the other hand, the clinical heterogeneity and the polygenic nature of SpA is quite different from classical autoinflammatory diseases such as familial Mediterranean fever. The related debate on whether the immune response in SpA is directed to an autoantigen or an exogenous antigen remains unresolved since identification of the causal arthritogenic antigen remains elusive, but research on the gut microbiome in SpA has begun to

elucidate the complex question of gut-derived antigens and metabolites in this disease [1]. Recent studies have identified an essential role of the gut microbiome in normal immune homeostasis by providing the host with a broad array of immunoreactive molecules. Metabolites derived from gut microbes can in turn contribute to communication between microbial species and host cells. Alteration in the microbial species in the gut (referred to as *dysbiosis*) observed in SpA is associated with altered microbial metabolites which may fundamentally modulate the disease pathogenesis. The interface of gut microbiome with host immunity has also stimulated interest in probing the cellular basis of the gut-joint axis [2]. There is compelling clinical and experimental evidence to support the notion of cross-talk between gut inflammation and joint inflammation. Recent studies in inflammatory bowel disease (IBD) have uncovered a critical role for integrins in directing gut-derived cell trafficking, with the collateral benefit of developing anti-integrin biologics for IBD. Recent characterization of synovial fluid T cells in SpA has identified integrin-expressing CD8+ T cells with transcriptomic and proteomic profile which closely mimics similar cells in the gut mucosa. These cells also demonstrate a restricted T cell receptor profile, which provides indirect support for an antigen-driven process and may shed light on the contribution of MHC I to SpA pathogenesis.

Studies on the structural alteration of target tissues in SpA suggest that the gut-joint axis be rephrased as a gut-enthesis axis, in view of the critical role of the synovial-entheseal complex in SpA pathogenesis [3]. These studies are beginning to shed light on one of the most distinctive pathological features of SpA, namely, new bone formation at sites of inflammation. The enthesis is subject to mechanical stress with resultant tissue microdamage, inflammation and repair. The normal enthesis harbours an array of immune cells including ILCs, $\gamma\delta$ T cells, conventional CD4+ and CD8+ T cells and myeloid lineage cells capable of local production of prostaglandins, growth factors and cytokines including TNF- α and IL-17. There is a fine balance of physiological tissue homeostasis and over-activity of these cytokines, the latter setting the stage

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for stress-induced inflammatory and subsequent osteoproliferation.

Defining the immunopathology of enthesal tissues as well as target sites such as the sacroiliac joints has been challenged by the relative inaccessibility of these tissues, particularly in axial SpA. In this regard, animal models have provided a more controlled setting to define basic immune mechanisms in SpA [4]. The HLA-B27 transgenic rat is one example of capitalizing on insights from genetic research in SpA to develop translational studies to evaluate immune consequences of genetic elements conferring susceptibility to SpA. This transgenic model has shed light on aberrant innate and adaptive immunity, as well as the role of the gut microbiome, in SpA pathogenesis. Other models such as the SKG mice have provided mechanistic models addressing how the IL-17/IL-23 axis mediates joint inflammation. The recently reported HLA-B27 transgenic *Drosophila* model has introduced new concepts into SpA pathogenesis, including a focus on the TGF β /BMP family of mediators.

Ongoing studies in the genetics of SpA continue to provide insights into the biologic basis of SpA, as well as the potential utility of genetic profiling in diagnosis and targeted therapeutics [5, 6]. Recent advances in psoriatic arthritis (PsA) have highlighted both the clinical heterogeneity of this disease, constituting a challenge for identifying common pathogenic pathways, as well as the polygenic nature of the disease. Since most patients with PsA also have psoriasis, it is difficult to dissect which genetic factors are associated specifically with joint disease vs skin disease. Studies in genetics and epigenetics have identified MHC and non-MHC variants, but pathways which are specific to PsA have been few in number. It may be that genetic factors are the dominant influence in psoriasis, while environmental factors such as trauma or infection drive the joint inflammation. Large, well-phenotyped cohorts with multi-omic technologies applied to biospecimens provide the best chance of resolving this complexity. The strongest genetic association in SpA is that of HLA-B27 with ankylosing spondylitis (AS). Recent studies implicate an interaction between HLA-B27 and the bone morphogenetic protein pathway receptor subunit ALK2, which might shed light on the propensity for new bone formation in AS as well as expanding the Th17 cell population. New bone formation could also be attributable to intracellular effects of misfolded HLA-B27, which in osteoblasts contribute to increase in expression of tissue non-specific alkaline phosphatase. Increased TNAP expression in osteoblasts was linked to increased mineralization in vitro, and bone formation in vivo.

Genome-wide association studies (GWAS) identified key genes in addition to HLA-B27 that are distinctively associated with AS [7]. Notable amongst these are endoplasmic reticulum aminopeptidase (ERAP) 1 and ERAP2, which encode proteins central to peptide processing and presentation. Polymorphisms in these genes may sculpt the peptidome

presented by HLA-B27. Aberrant peptide processing may also give rise to the accumulation of unstable protein complex in the ER, which could drive ER-associated protein degradation (ERAD), the unfolded protein response (UPR) and subsequent activation of autophagy.

The strong association of MHC1 with AS has always suggested to immunologists a role for CD8+ cytotoxic T lymphocytes (CTL) in this disease. But the contribution of such cells to immune activation and inflammation in AS has proved difficult to resolve. Recent advances in the biology of CTL in cancer and infection have introduced new approaches to this question in AS [8]. These studies in AS have demonstrated enrichment of CTL-related genes in GWAS, expansion of potentially pathogenic CTL in synovial lymphocyte populations and clonal expansion of CTL. There is also evidence of immune dysregulation of CTL in AS, whereby cytolytic protein expression demonstrates an uncoordinated signature. This may set the stage for disruption of CTL homeostasis reflected in a failure to drive these cells into an exhausted phenotype. But the *dramatis personae* in this play certainly involves a cast of characters well beyond CD8+ and CD4+ T lymphocytes [9]. This includes mesenchymal stromal cells, fibroblast-like synoviocytes, type 3 innate lymphoid cells, MAIT cells and iNK T cells. Better characterization of these pathogenic cells could lay the groundwork for new targeted therapies, which could control the inflammatory process and the upstream pathways that trigger immune dysregulation and subsequent bone formation in AS. Similarly, in PsA there is growing recognition of a wide array of cells contributing to inflammation and damage [10]. The efficacy of IL-17 targeted therapies have heightened interest in the interaction of Th17 cells and monocytes. Tissue-resident T cells may play a critical role in the interface of entheses and bone, a target site for inflammation in PsA. Cytokine effects on local stromal cells and epithelial cells are also proving to be an informative line of investigation in PsA. These studies are effectively exploiting technical advances in cell biology, such as CyTOF and single-cell RNA sequencing. This bodes well for future studies in SpA as researchers zero in on the precise mechanisms initiating and perpetuating the inflammatory assault on joint and skin tissues. This may well usher in a period of innovative therapeutics with curative potential.

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