Immune-Mediated Arthritis: Molecular Mechanisms and Comparative Pathology

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Immune-mediated Arthritis in Humans

Humans suffer from several immune-mediated arthritides. These diseases are segregated based mainly by their clinical features and patterns of joint involvement, as their underlying mechanisms are different. Rheumatoid arthritis (RA) is characterized by erosions of small joints, particularly those of wrists (intercarpal joints), ankles (intertarsal joints), and digits (metacarpal, metatarsal, and proximal interphalangeal joints). The effects are restricted chiefly to synovial joints in the appendicular skeleton and typically exhibit bilateral symmetry. Swelling is limited to the region immediately adjacent to the inflamed joint. Bone loss at the joint margins and beneath the articular cartilage may be extensive. Generally, new bone does not form, although in rare instances severely eroded (end-stage) joints may fuse. The primary anatomic features are chronic proliferative synovitis with eventual formation of pannus (a fibrovascular tissue that erodes bone and joint cartilage). Extra-articular lesions include necrotizing vasculitis, rheumatoid nodules, and osteoporosis.

In contrast, psoriatic arthritis (PsA) and ankylosing spondylitis (two representative forms of spondyloarthropathy) are distinguished from RA by enthesitis (inflammation of the muscle and tendon attachments) and may involve the axial skeleton as well as appendicular sites. In the distal limbs, swelling is not limited to the joints, resulting in relatively uniform thickening of the digits (“sausage digits”). Affected spinal joints often feature formation of bony bridges (ankyloses) between vertebral bodies. Erosions peripherally can be extensive, with new bone formation and bone spurs at the sites of muscle and tendon attachment. Extra-articular manifestations include uveitis and cutaneous plaques.

Spontaneous Immune-mediated Arthritis in Animals

Immune-mediated arthritis is seldom encountered in animals. Chronic RA has been reported in dogs [9] with a specific genotype that mimics a genetic predisposition in humans [23]. Spondyloarthritis resembling psoriatic arthritis and ankylosing spondylitis have been described in gorillas [26] and rhesus monkeys [25]. Immune-mediated arthritis develops spontaneously in female MRL/lpr mice by about five months of age [16].

Induced Models of Immune-mediated Arthritis in Animals

Humans are an outbred population, so each individual with immune-mediated arthritis develops an essentially unique condition. In contrast, experimental animals are usually inbred populations, which allow different forms of arthritis to be studied in individuals with a homogeneous genetic background. Thus, animal models that both reproduce the anatomic and clinical features of human immune-mediated arthritides and can be incited by the simple administration of an antigenic stimulus are of considerable interest, both as models for dissecting the pathogenesis of the human diseases and as platforms for testing the efficacy of novel therapeutic candidates.

A plethora of animal models have been developed for these purposes. Many epitopes can kindle immune-mediated arthritis in susceptible strains of mice, rats, or nonhuman primates, including heterologous type II collagen (a principal component of articular cartilage), whole heat-killed bacteria or bacterial byproducts, certain chemicals, and many proteins (reviewed in [20]). The transplantation of RA synovium into immunodeficient mice also can provide a means for dissecting basic disease mechanisms [11]. In many research laboratories, the experimental models of choice are rodents in which the immune-
mediated arthritis has been produced using either intact, heat-killed mycobacteria or type II collagen. This preference arises from the rapid onset and reproducible course of clinical disease as well as the broad literature database available for these models.

Adjuvant-induced arthritis (AIA) has been investigated in rats for several decades [12,24]. One common model is to inject heat-killed mycobacteria in a viscous adjuvant at the tail base. Arthritis occurs on a predictable schedule, with almost all animals developing hind paw swelling after a latent period of 9 to 10 days. Hind paw lesions usually are bilaterally symmetrical; the fore paws typically are unaffected until later during the course of disease. The peak impact on the tarsal joints occurs by 7 days after disease onset, at which time the bone marrow and peri-articular soft tissues are packed with lymphocytes and macrophages. Neutrophils may or may not be prominent in the sub-synovial soft tissue and joint cavity. Myriad osteoclasts line the eroding endosteal surfaces; bony trabeculae are almost completely lacking in affected bones, and the thickness of the cortical and subchondral bone plates may be markedly diminished as well. At the same time, coalescing osteophytes cover periosteal surfaces. Joint cartilage is morphologically intact, although application of toluidine blue reveals extensive loss of proteoglycans in the cartilage matrix. Where cartilage is eroded, the usual cause is erosion of subchondral bone with extension of inflammatory cells in bone marrow through the cartilage from below 6. Growth of pannus into the joint cavity, leading to direct destruction of cartilage, is a less pronounced change in this model. Interestingly, AIA in rats is a systemic disease. Chronic inflammatory foci disrupt or efface the architecture of many other organs, including the eye (uvea), kidney, and spleen.

Collagen-induced arthritis (CIA) is a more recent development [8,10,14,28]. In a typical setting, mice or rats receive one or more intradermal injections of collagen. Arthritis develops in from 40% to 80% of immunized animals after a variable latent period of 2 to 3 weeks; the lack of predictability generally requires that animals be enlisted into studies on a rolling basis, which slightly complicates the study design. However, in some strains the incidence of CIA is essentially 100% [18,30]. Both fore- and hind-paws are affected, but the impact on hind paws often is more pronounced. The joint lesions may or may not exhibit bilateral symmetry. The typical progression of lesions – proliferative synovitis followed by expansion of pannus leading to erosion of cartilage and subchondral bone [18] – morphologically is more reminiscent of RA than is AIA. Again, CIA lesions peak at 7 days after disease onset. Osteoclasts are common in CIA, but less so relative to AIA. This difference is reflected in the partial preservation of bone trabeculae and subchondral bone in animals with CIA. New bone formation on the periosteal surface is present, but the extent is less marked than that of AIA. Pannus within the joint cavity is a common feature of CIA, and the underlying cartilage is extensively eroded. In contrast to AIA, inflammatory lesions in CIA are localized to joints and do not extend to other organs.

**Molecular and Cellular Pathogenesis of Arthritis**

Current dogma holds that RA and other immune-mediated arthritides result from an imbalance in intercellular signaling cascades localized within the joint [5,13]. Under normal circumstances, actions of cytokines with pro-inflammatory roles (such as interleukin-1 [IL-1], IL-6, IL-8, IL-12, IL-15, IL-18, and tumor necrosis factor-α [TNF]) are in functional equilibrium with those of anti-inflammatory cytokines (including IL-4, IL-10, IL-11, IL-13) and endogenous cytokine inhibitors (IL-1 receptor antagonist [IL-1ra], IL-18 binding protein, and soluble receptors for IL-1 and TNF). Immune-mediated arthritis is initiated when the immune system begins to respond to an intra-articular antigen by producing pro-inflammatory cytokines in sufficient quantities to overcome the dampening actions of the anti-inflammatory molecules (a Th1-weighted pattern; [22]). Pro-inflammatory mediators initiate and maintain inflammation directly through their action on synovial cells and infiltrating inflammatory cells; in arthritis, the process exists as a poorly regulated, local, positive-feedback system as these cytokines are secreted by activated T-helper lymphocytes and macrophages that migrate into the inflamed region as well as by the activated synovioocytes in the affected joint. The same pro-inflammatory molecules drive joint erosion indirectly by causing the activated inflammatory cells to produce the osteoclast-inducing molecule receptor activator of nuclear factor κB [RANKL]. Finally, pro-inflammatory cytokines also induce myriad other molecules that either enhance leukocyte recruitment (e.g., leukotrienes, prostanoids) or directly damage the articular surface (reactive oxygen species, matrix metalloproteases).

The two dominant pro-inflammatory cytokines in RA are IL-1 and TNF [1,4]. Both are co-expressed widely during acute and chronic arthritis and act synergistically to incite and sustain inflammation and erosion in arthritic joints. In animals, either IL-1 [2,12] or TNF [12,21] alone can drive arthritis. However, the functions of these two cytokines, while overlapping, are not identical, as growing evidence suggests that joint inflammation may be mediated chiefly by TNF, while skeletal destruction appears to be impelled by IL-1 (reviewed in [29]). These discrepancies might explain the divergent responses of RA patients to anti-arthritis therapies, as RA represents a patient-specific syndrome rather than a uniform condition. A logical explanation for this situation is that RA in some people is driven by IL-1, in others by TNF, and in still others by additional cytokines.
This premise is supported by the demonstration that IL-6 rather than IL-1 or TNF is the predominant factor in dogs with rheumatoid-like arthritis [7].

Activated B lymphocytes that make autoantibodies to antigens from intra-articular molecules also play a role in rheumatoid arthritis [31]. The B-cell activity is mediated by T-cells that share the same antigen specificity. In animals, this pathogenesis is shown by the occurrence of immunoglobulin-mediated synovitis in transgenic K/BxN mice [19].

A genetic predisposition to contract autoimmune disease exists in humans. To date, the strongest such susceptibility is to develop spondyloarthopathies [17]. More than 90% of the patients who acquire such conditions harbor the HLA-B27 gene, a human leukocyte antigen (HLA) which encodes a particular form of β2 microglobulin (which acts as the invariant portion of class I major histocompatibility complex that presents antigens to T-cells [3]). The importance of this genetic predilection in RA is confirmed by the genesis of immune-mediated arthritis in transgenic rats that carry HLA-B27/β2m [15]. Interestingly, autoimmune arthritis is often linked with immune-mediated intestinal inflammation in animal models [27]. This susceptibility seems to arise from interactions between the immune system and intestinal bacteria (or their byproducts), possibly as a result of molecular mimicry between molecules expressed by the bacteria and HLA-B27.

Summary

Immune-mediated arthritis in humans and animals share many clinical, structural, and mechanistic features. Therefore, information of relevance to the pathogenesis and treatment of human conditions can be acquired with reasonable success using experimental animal models. Rodents (especially some rat strains) are of particular interest in such studies due to their homogenous genetic background, reproducible disease patterns, and large historical database.

References


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