

# Antibody-dependent and -independent mechanisms of inflammatory arthritis

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**Inflammatory arthritis encompasses a set of common diseases characterized by immune-mediated attack on joint tissues. Most but not all affected patients manifest circulating autoantibodies. Decades of study in human and animal arthritis have identified key roles for autoantibodies in immune complexes and through direct modulation of articular biology. However, joint inflammation can arise because of pathogenic T cells and other pathways that are antibody-independent. Here we review the evidence for these parallel tracks, in animal models and in humans, to explore the range of mechanisms engaged in the pathophysiology of arthritis and to highlight opportunities for targeted therapeutic intervention.**

## Introduction

Inflammatory arthritis affects approximately 1% to 2% of the population (1). Although dwarfed numerically by osteoarthritis, its collective impact remains substantial because of the potential for severe disability and because patients are often young. The most common adult form of inflammatory arthritis, rheumatoid arthritis (RA), can begin in teenagers, whereas juvenile idiopathic arthritis (JIA) peaks before the age of 6 years. This family of diseases therefore disproportionately threatens a period of life typically characterized by good health, leading to impaired quality of life as well as loss of productivity and medical expenses.

Inflammatory arthritis is not a single disease. Broadly, inflammatory arthritis may be divided into conditions focused on the synovium and those that also affect the entheses, the insertion zones of tendons, ligaments, and joint capsules into bone. This division is far from absolute but usefully reflects a clinical and pathophysiologic spectrum that ranges from RA, characterized by an aggressive synovitis affecting peripheral joints, to ankylosing spondylitis, characterized by enthesitis and new bone formation in the axial skeleton. Ankylosing spondylitis, reactive arthritis, and psoriatic arthritis form part of a family of entheses-focused diseases termed “spondyloarthritis.” Arthritis beginning in childhood was traditionally regarded as a distinct disease family, although it is increasingly clear that most forms of JIA resemble their adult counterparts (2). This Review will focus on synovitis and its genesis and perpetuation by antibodies and antibody-independent mechanisms. Mechanisms of spondyloarthritis have been recently reviewed (3).

## Autoantibodies in inflammatory arthritis

In common with other autoimmune diseases, many forms of inflammatory arthritis are associated with circulating autoantibodies (Table 1 and refs. 4–10). In 1939, serum from a patient with RA was noted to aggregate sheep red blood cells opsonized with rabbit IgG (11). This serologic capacity was subsequently found in many but not all RA patients and determined to reflect the presence of RF, an antibody directed against the fragment crystallizable (Fc) region of IgG (12, 13). Although detectable in other disease states, RFs associated with RA exhibit affinity maturation of the antibody complementarity-determining region, potentially implicating a history of T cell help that is uncommon for RF generated outside of RA (14–18). Clinically, RA accompanied by RF — termed “seropositive RA” and representing 40% to 80% of all RA — is characterized by a tendency toward greater disease severity (19–22). RFs are a heterologous group of antibodies, most commonly IgM but also IgG or IgA. Although RF of all isotypes is associated with more aggressive disease and bone erosions, IgA RF is particularly correlated with extra-articular manifestations, such as interstitial lung disease, nodule formation, and rheumatoid vasculitis (23–27).

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**Table 1. Autoantibodies in RA**

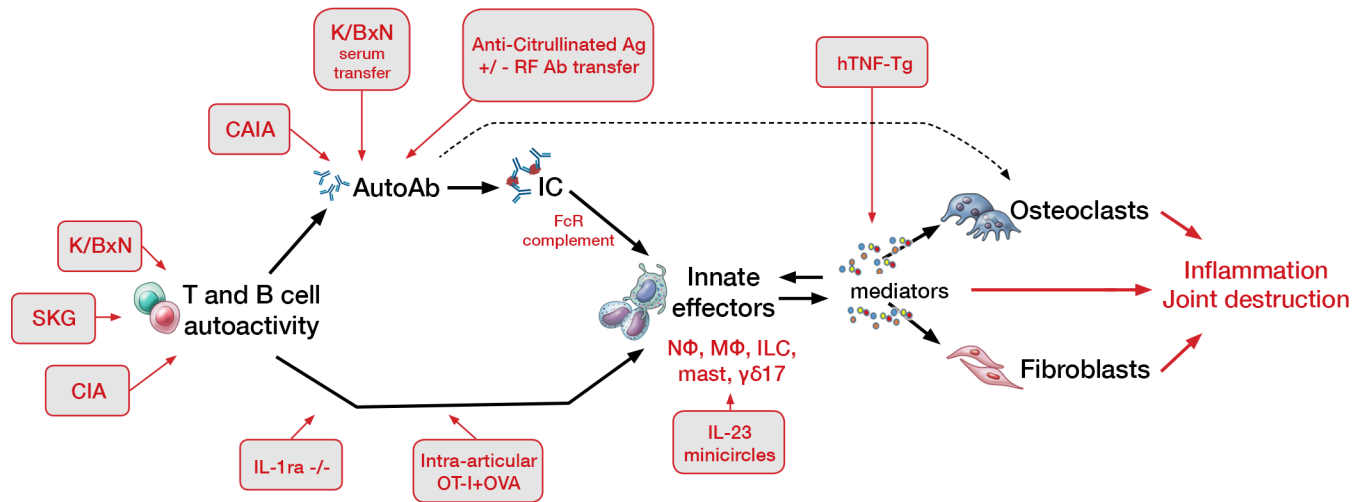
Autoantibodies	Prevalence	Citation
Rheumatoid factor (RF)	41%–80%	20, 21, 46, 48
Anti-citrullinated proteins (ACPAs)	36%–78%	20, 21, 31, 48
Citrullinated fibrinogen	25%	4
Citrullinated vimentin	57%–61%	38, 46
Citrullinated aldolase A	35%	4
Citrullinated collagen type II	7%–24%	185, 186
Citrullinated $\alpha$ -enolase	70%	4
Citrullinated RA33	44%	10
Anti-carbamylated proteins (anti-CarPs)	27%–45%	5, 21, 187
Carbamylated albumin	31%	188
Carbamylated fibrinogen	38%–43%	189, 190
Carbamylated $\alpha$ 1-antitrypsin	N/A <sup>a</sup>	191
Carbamylated vimentin	35%	46
Anti-malondialdehyde-acetaldehyde adducts	88%–93%	6, 48
Anti-peptidyl arginine deiminase 4 (anti-PAD4)	18%–42%	36–38
Anti-RA33 (hnRNP A2/B1)	5%–35%	10, 19
Anti-nuclear antibody (ANA)	34%	50
Anti-histone	15%–75%	4, 7, 8
Anti-DEK	57%	9
Anti-native collagen type II	17%–43%	192, 193
Anti-oxidized collagen type II	45%	47
Anti-GPI	12%–25%	194
Anti-acetylated vimentin	37%	46

<sup>a</sup>Antibodies detected but percentage prevalence data are not available. This is a partial list and is not intended to be comprehensive account of all autoantibodies in RA.

The identification of RF spurred the search for other RA-associated autoantibodies. One of the first antigen-specific autoantibodies was discovered in 1964, when serum from some RA patients was shown to bind in a perinuclear pattern to human epithelial cells cultured from buccal mucosa. This autoantibody was named “antiperinuclear factor” (28). Reactivity was subsequently noted against the keratin layer of rat esophagus (29). These antibodies were directed against peptides modified posttranslationally through conversion of arginine to citrulline, an enzymatic reaction executed by the peptidyl arginine deiminases (PADs) that neutralizes the positive charge of the arginine side chain (30–32). Such ACPAs are highly specific for RA and are present in approximately two-thirds of patients (33). ACPAs recognize citrullinated fibrinogen, vimentin, enolase, and collagen peptides, among other antigens (Table 1). Indeed, ACPAs often recognize multiple citrullinated targets because affinity is driven by the citrulline residue itself, modulated only modestly by peptide context (34). For reasons still to be determined, RF<sup>+</sup> and ACPA<sup>+</sup> patient subsets largely overlap, with ACPA reactivity often preceding the appearance of RF (35). Intriguingly, the citrullination pathway is also targeted by other RA autoantibodies, with approximately 20% to 40% of RA patients manifesting antibodies against PAD4 (36–38). These patients may exhibit more joint erosion, while RA patients with anti-PAD4/PAD3 antibodies demonstrate more interstitial lung disease (37, 39, 40).

Both RF and ACPAs can be generated within the synovium, as evidenced both by higher levels in the synovium and synovial fluid than in paired blood and by the presence of corresponding plasma cells in joint tissue (41–43). Local autoantibody production is likely fostered by a recently identified lymphocyte, the T peripheral helper (T<sub>PH</sub>) cell, which provides help for B cells outside of lymph nodes (44). ACPAs can also be generated in the lung, supporting the possibility that RA can begin as an immune reaction in the pulmonary epithelium that extends to affect the joints (45).

Other autoantibodies have been associated with inflammatory arthritis. Approximately 45% of RA patients exhibit antibodies against peptides that have undergone another posttranslational modification, carbamylation (5). Antibodies may be formed against proteins modified through acetylation, oxidation, or malondialdehyde-acetaldehyde adducts (46–48). IgG isolated from RA joints exhibits reactivity against histones (49). ANA is common and in RA is associated with concomitant Sjogren’s syndrome (50). In JIA,



**Figure 1. Intersection of murine arthritis models with the pathogenic sequence of inflammatory arthritis.** Inflammation in murine arthritis can arise through immune dysfunction arising at a wide variety of levels, ranging from errant T and B cell-driven antigen targeting to overexpression of downstream inflammatory mediators. Autoimmunity can translate into arthritis via antibody-dependent pathways, typically through IgG and immune complexes (ICs), but also independent of autoantibodies through the action primarily of pathogenic T lymphocytes. Murine models (red-lined gray boxes) illustrating each respective mechanism are indicated. CAIA, collagen antibody-induced arthritis; FcR, Fc $\gamma$  receptor; C', complement; Cit, citrullinated peptide; OVA, ovalbumin; N $\phi$ , neutrophil; M $\phi$ , monocyte/macrophage; ILC, innate lymphocyte; mast, mast cell; hTNF-Tg, human TNF-transgenic. Modified from Monach et al. (184). Illustrated by Mao Miyamoto.

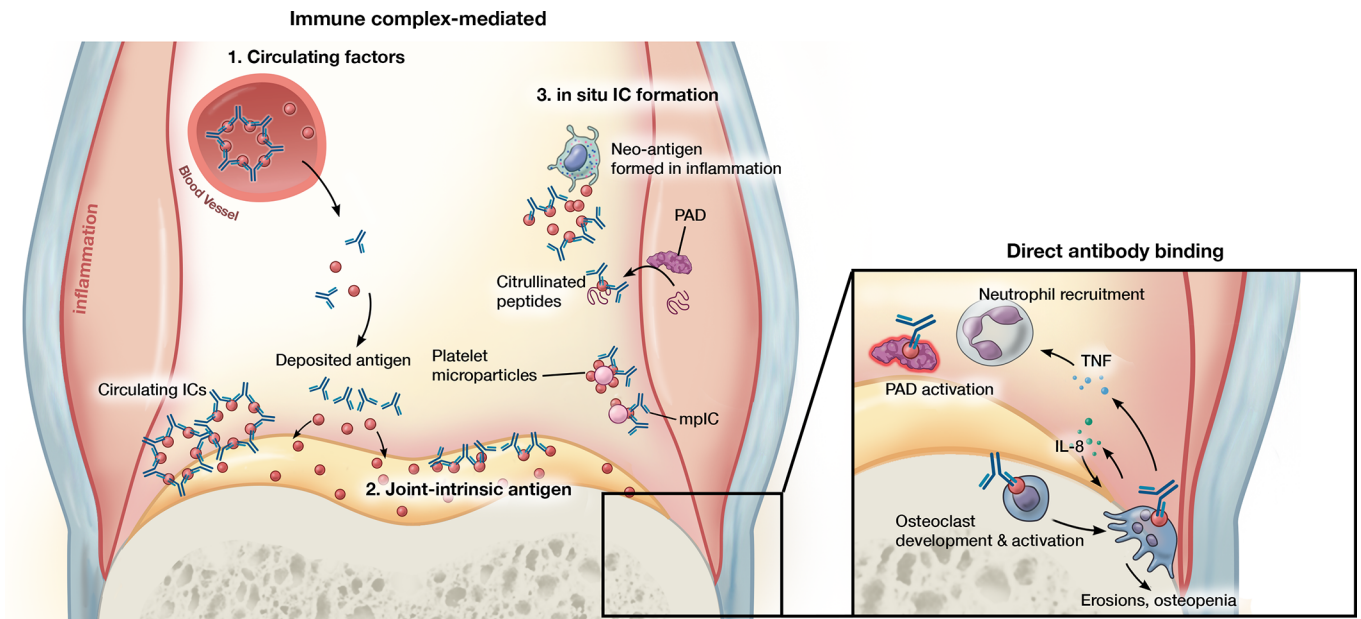
the presence of ANA correlates with early disease onset and risk for chronic anterior uveitis, especially when anti-histone antibodies are also present (7, 8, 51, 52). Oligoarticular JIA with uveitis has also been associated with antibodies against the chemoattractant nuclear protein DEK (9).

The pathogenic relevance of antibodies is amply confirmed in animals. The 2 best-studied experimental arthritis models, K/BxN arthritis and collagen-induced arthritis (CIA), are both mediated primarily through IgG. The K/BxN mouse is a cross (x) between mice bearing the KRN-transgenic T cell receptor in a C57BL/6 background (K/B) and the nonobese diabetic (NOD) mouse (N). The KRN receptor recognizes bovine ribonuclease as presented by the class II major histocompatibility complex (MHC) molecule A<sup>k</sup>. However, in the context of the NOD MHC II, termed I-A<sup>b7</sup>, this receptor instead recognizes a peptide from the glycolytic enzyme glucose-6-phosphate isomerase (GPI). Resulting anti-GPI antibodies engender arthritis with clinical and histopathologic similarities to RA, including symmetry, a distal-to-proximal gradient of severity, formation of erosive pannus, and accumulation of neutrophils in the joint. In CIA, mice immunized with allogenic type II collagen produce antibodies reactive against articular cartilage. In both K/BxN and CIA systems, joint disease can be induced in naive wild-type mice via antibody transfer, without additional contribution from adaptive immunity (Figure 1 and refs. 53–60). Adoptive transfer of ACPAs can further intensify synovitis, supporting a pathogenic role for these autoantibodies (61, 62).

### Mechanisms of antibody-mediated arthritis

Arthritis mediated by IgG arises via distinct pathways that can be divided into 2 categories based on the role of ICs (Figure 2). We will review each category in turn, recognizing that individual patients with arthritis may proceed simultaneously via both mechanisms as well as through IgG-independent pathways, discussed subsequently.

**IC-mediated arthritis.** ICs are aggregates of antibodies around a multivalent target and may contain IgG, IgM, and sometimes IgA. Antibody clustering engages low-affinity IgG Fc receptors and induces conformational changes in the Fc region that permit IgG to activate complement, a process termed “complement fixation.” The complement system was originally identified as a soluble component of serum able to “complement” antibody-induced lysis of bacteria and consists of a set of proteins with multiple immune functions. These proteins are the anaphylatoxins (C3a and C5a) that mediate inflammation, vasodilation, and chemotaxis; opsonins (C3b and C4b) that can bind to ICs to facilitate clearance by cells bearing complement receptors; and the membrane attack complex (MAC, C5b–C9) that forms transmembrane pores in target cells to induce osmotic lysis. Complement can be activated through 3 pathways. The classical pathway is initiated by



**Figure 2. Antibody-mediated mechanisms of inflammatory arthritis.** Joint inflammation mediated by antibodies can proceed via distinct and not mutually exclusive pathways. ICs formed in circulation can precipitate in joint tissue and trigger enhanced vascular permeability that enables entry of pathogenic antibodies into the joint. ICs/antibody clusters can form within the joint through binding to joint-intrinsic antigens such as collagen, blood-borne antigen deposited on cartilage, or antigens formed de novo in the inflamed milieu such as citrullinated peptides and platelet microparticles, the latter generating microparticle-associated immune complexes (mpICs). Independent of IC formation, antibodies can mediate pathology via binding to specific targets. For example, antibodies promote citrullination by altering the activation threshold of PADs and stimulate the development or activation of osteoclasts. In addition to promotion of bone erosions and local osteopenia, osteoclasts may promote further osteoclastogenesis and contribute to neutrophil recruitment via IL-8 and other mediators. Illustrated by Mao Miyamoto.

the Fc portions of antigen-bound IgG, IgM, and sometimes IgA through complement proteins C1q/r/s, C4, and C2. The alternative pathway relies upon the spontaneous hydrolysis of complement component C3 into C3b, which binds to and cleaves factor B to generate a C3 convertase that is key to completing the complement cascade and forming the MAC. The lectin pathway is homologous to the classical pathway but is activated by lectins, carbohydrate-binding proteins that recognize specific glycans, linking to the C3 convertase and its downstream effector pathways via mannose-binding lectin-associated serine proteases (MASPs) (63).

Accumulation of ICs in joints occurs in 3 ways (Figure 2). Circulating ICs may deposit directly in joint tissue. Alternately, antibodies against clustered joint-intrinsic antigens may form ICs locally. Finally, antibodies may encounter antigen deposited in the joint from the circulation or generated within the joint itself, again resulting in local IC formation. ICs are likely a major route to human joint inflammation, particularly in seropositive RA, as suggested by the high prevalence of synovial fluid complement fixation, ICs within synovial fluid neutrophils, and ICs in joint explant tissue from this RA subset (refs. 64–66 and Table 2).

The capacity of RF to bind multiple IgG molecules at once can promote IC formation. Self-aggregated RF as well RF bound to IgG activates complement (67–70). Correspondingly, RF is common in ICs isolated from RA joints (68, 71–75). RF inhibits the ability of complement to break up ICs and can link smaller complexes together into larger, less soluble ones, potentially accounting for the observations that RF is found in most RA patients with vasculitis and depressed serum complement and that synovial fluid neutrophils containing ICs are observed primarily in seropositive patients (66, 76–78). RF amplifies cell activation by ICs containing ACPAs and citrullinated target peptides, and patients with both RF and ACPAs exhibit higher disease activity and circulating proinflammatory mediators than those with either autoreactivity alone (20, 22, 79). The nucleating antigen may also play a key role. Citrullinated fibrinogen is a common component of circulating ICs in ACPA-positive RA patients. Although ICs can activate macrophages by cross-linking Fc $\gamma$  receptors, synovial macrophages also bear Toll-like receptor 4 (TLR4), an innate immune receptor that recognizes conserved microbial products but also fibrinogen. Therefore, ICs containing citrullinated fibrinogen synergistically activate Fc $\gamma$  receptor and TLR4 pathways to trigger an inflammatory response (80). Of note, transfusion of RF-containing plasma from patients with RA into

**Table 2. ICs in RA tissues**

Study	Tissue	Source	n	RF*	Detection	IgG%	C3%	IC% <sup>A</sup>	Citation
Fish	Synovium	Bx, Ar	7	57%	IF	100	71	71	195
Rodman	Synovium	Bx	8	75%	IF	100	100	100	196
Brandt	Synovium	Bx, Ar	10	80%	IF	80	80	80	197
Bonomo	Synovium	Bx	10	70%	IF	100	100	100	198
Ghose	Synovium	Bx, Ar	21	62%	IF	67	62	62	199
Cooke	Cartilage	Bx	42	69%	IF	90	93	83	150
Ugai	Cartilage	Ar	12	NR	IF	75	75	75	200
Vetto	Cartilage	Ar	34	54%	IF	65	48	48	201

Bx, synovial biopsy; Ar, arthroplasty; NR, not reported; IF, immunofluorescence microscopy. <sup>A</sup>Defined by colocalized immunoglobulin and complement. These studies evaluated the presence of immunoglobulins and complement deposited in joint tissues obtained from patients with RA. This table highlights representative studies and is not intended to represent a complete list.

nonarthritic human recipients (!) failed to yield joint inflammation (81). Further, RF may appear years before the onset of clinical symptoms, confirming that RF alone is not sufficient to develop RA (35, 82).

IC-mediated arthritis is among the best-understood arthritis pathways because of the availability of tractable animal models. Both CIA and K/BxN arthritis arise via ICs. In CIA, clusters of IgG form on type II collagen in the joint (56–58). In K/BxN arthritis, joint specificity despite the ubiquity of the autoantigen is thought to arise through deposition of positively charged GPI onto the negatively charged cartilage surface, followed by in situ IC formation, likely with ICs deposited from the circulation (53–55, 83, 84). The requirement for ICs is clear from the fact that multiple antibodies recognizing nonoverlapping epitopes are generally required (59, 60, 85). Entry of autoantibodies is facilitated by vascular leakiness of the synovial vasculature induced by the binding of ICs to circulating neutrophils and platelets as well as perivascular mast cells, leading to the release of vasoactive mediators, such as TNF- $\alpha$ , histamine, and platelet-derived serotonin (86–88). Inflammation then proceeds through activation of cells via low-affinity IC receptors (in mouse, receptors Fc $\gamma$ RIII and Fc $\gamma$ RIV) together with the receptor for anaphylatoxin C5a (19, 89–94). Cells implicated in immune sensing include neutrophils, mast cells, and potentially macrophages, with C5a serving to sensitize cells to Fc $\gamma$ R-mediated activation and to arrest neutrophils on the synovial endothelium (95–99). Inflammation is then mediated by infiltrating neutrophils and monocytes together with local cells, including fibroblasts and macrophages (86, 100–105).

Despite the key role of the classical pathway in IC recognition and clearance, classical pathway components C1q, C2, and C4 are not required for IgG-mediated arthritis in the mouse. Rather, the alternative pathway is dominant, and murine arthritis is markedly attenuated in the absence of C3 or factor B (89, 106–108). The mechanistic basis for this observation is incompletely understood. IgG is not canonically considered to activate the alternative pathway, although in fact such activation has been reported for murine IgG, human ACPAs, and human IgA (109–111). Murine studies reveal at least 2 related mechanisms. IgG immobilized on cartilage triggers cleavage of alternative pathway component factor D via lectin pathway MASP-1/3 (MASP-1 and MASP-3 are splice variants of a single gene and so difficult to distinguish genetically) (112, 113). Correspondingly, mice lacking MASP-1/3 are resistant to CIA (114, 115). Another lectin pathway protease, MASP-2, activates C3 via the “C4/C2 bypass pathway,” a poorly defined pathway whereby C3 is cleaved without requiring C2 and C4, components of the typical lectin pathway C3 convertase. Mice deficient in MASP-2 are partially resistant to CIA (116). How pathogenic IgG engages MASPs remains to be defined, but deposition of ICs likely represents a key step. The role of complement in arthritis has recently been comprehensively reviewed (63).

A further line of evidence for the role of ICs and complement in arthritis arises from studies of cartilage. Clinical observation shows that arthritis often recurs in RA joints subjected to synovectomy but tends to abate in joints from which all cartilage has been resected, even if synovium remains (117–119). The articulating surface of cartilage lacks a bilipid membrane, and as a result complement inhibitory proteins such as CD59 are absent. Complement fixation is constrained by less efficient chemical mechanisms, such as surface sialic acids, and by the maintenance of very low levels of complement in normal synovial fluid (64, 120). As complement factors enter the joint from the blood in the context of inflammation-mediated vascular leak,

the cartilage surface becomes the focus of poorly controlled complement fixation, including via the alternative pathway (63, 113). Further, ICs deposited or formed on cartilage must be cleared by inflammatory cells recruited into the joint, and neutrophils encountering ICs can discharge their granule enzymes directly into the cartilage surface in a potentially injurious process termed “frustrated phagocytosis” (121). Consistent with this biology, in murine arthritis, antibody arthritogenicity correlates with cartilage binding (62, 122). It is therefore likely that the cartilage surface explains why IC-mediated inflammation in RA manifests predominantly in the joints — in other words — why RA is an arthritis at all.

Indeed, ongoing formation of ICs within the joint likely represents a key mechanism of disease chronicity. In the transient arthritis of serum sickness, joint inflammation resolves once the shower of ICs subsides. In chronic inflammatory arthritis, autoantibodies recognizing antigens that are formed or released in the inflamed joint, such as citrullinated peptides and DEK, generate an amplification loop whereby joint inflammation begets ICs that in turn perpetuate joint inflammation. Feeding into this cycle, IC-mediated MAC deposition on synovial fluid neutrophils hyperactivates intracellular PADs to generate citrullinated RA autoantigens (123–125). Microparticles are another source of locally generated ICs. Murine and human studies implicate CD41<sup>+</sup> (GP1b<sup>+</sup>) microparticles released by platelets and potentially megakaryocytes as important mediators of joint inflammation, at least in part through IL-1 $\alpha$  and IL-1 $\beta$  (126, 127). Platelet microparticles feature citrullinated surface proteins recognized as RA autoantigens, including vimentin and fibrinogen. These microparticles nucleate many of the ICs found in RA synovial fluid, creating microparticle-associated ICs (mpICs) (Figure 2 and ref. 128).

*Glycosylation as a modulator of IgG effector function.* The ability of IgG to bind Fc receptors and fix complement depends on IgG Fc glycosylation. A short biantennary glycan, typically 7–13 monosaccharides in length, is attached to asparagine 297 in the C<sub>H</sub>2 region of each IgG Fc heavy chain. These 2 glycans interact with each other and with the protein backbone of the opposite heavy chain to modulate the structure of the Fc region. IgG lacking Fc glycans loses much of its effector capacity, and in vivo enzymatic removal abrogates antibody-mediated arthritis (129). Variation among the greater than 30 possible Fc glycoforms fine-tunes the ability of IgG to interact with ligands such as C1q, the human IC receptor Fc $\gamma$ RIIA, and mannose-binding lectin. Precise structure-to-function correlation remains controversial, both because experimental findings diverge and because murine and human systems overlap incompletely (130). In general, glycoforms with reduced galactose and sialic acid are thought to confer enhanced proinflammatory capacity, whereas highly galactosylated and sialylated IgG engage antiinflammatory mechanisms to skew IgG toward immunomodulatory function. Loss of sialylation represents a “molecular switch” that converts innocuous autoantibodies into antibodies capable of initiating murine arthritis (109, 131). Desialylation enables ICs to activate osteoclasts, thereby contributing to local and generalized bone loss (132). Patients with RA and JIA exhibit reduced galactosylation with more modest changes in sialylation, sometimes predating overt disease by months or years (133–136). ACPAs accompanying seropositive RA exhibit even more marked hypogalactosylation, as well as striking fragment antigen-binding (Fab) glycosylation of unknown functional significance (136–138).

Correlative evidence for an etiologic role of IgG Fc glycosylation in human RA comes from pregnancy. Pregnancy is accompanied by marked increase in circulating estrogen, the only factor known to modulate human IgG glycans in vivo through its capacity to enhance Fc galactosylation (139). Pregnancy is accompanied by a marked decrease in hypogalactosylated IgG, often corresponding temporally with an amelioration of RA disease activity. IgG glycosylation normalizes after parturition, again often coincident with flaring RA (140, 141). These intriguing correlations suggest that RA improvement in pregnancy may be mediated in part through IgG Fc glycosylation, although glycan shifts could still represent either an epiphenomenon or a result of reduced inflammation. Indeed, in the mouse, estrogen attenuates arthritis flare in postpartum mice with only modest changes in IgG galactosylation (142). It is possible, and even probable, that glycan changes both reflect the inflammatory milieu and alter IgG function to potentiate further inflammation. Further study will be required to define causality in the relationship between IgG glycan changes and arthritis in the human context.

*Arthritis mediated by IgG independent of ICs.* IgG can engender joint inflammation through the molecules that they target, without formation of ICs. ACPA-mediated activation of osteoclasts and antibodies that enhance PAD function are 2 examples (Figure 2).

ACPAs are among the strongest predictors of a destructive arthritis course (143, 144). Anti-citrullinated vimentin antibodies bind to osteoclasts, stimulating osteoclastogenesis and leading to increased bone resorption (145). The introduction of anti-citrullinated vimentin antibodies is sufficient to cause periarticular bone loss in wild-type mice as well as generalized osteopenia in lymphocyte-deficient *Rag-1*<sup>-/-</sup> mice (145, 146).

How ACPAs stimulate osteoclastogenesis remains unclear. Studies have implicated both direct binding to citrullinated vimentin on osteoclasts and desialylation-dependent engagement of low-affinity Fc receptors (132, 145). Other work implicated IL-8 elaborated by ACPA-stimulated osteoclasts, but the antibodies used were later found to lack citrulline specificity, implicating citrulline-independent stimulatory mechanisms (34, 147). IL-8 not only promotes further osteoclastogenesis but also is an important neutrophil chemoattractant, raising the possibility that osteoclasts play a role early in antibody-mediated inflammation as well as in later bone erosion, including but not limited to disease mediated by ACPAs.

Antibodies directed against PADs can also be pathogenic. PAD enzymes require supraphysiologic concentrations of calcium (5–10 mM *in vitro*) for optimal citrullination. Intracellular calcium concentrations rarely exceed 0.1 mM even with activation, while typical extracellular calcium concentrations approximate 1 mM (148). The binding of anti-PAD4 antibody increases the sensitivity of PAD4 to calcium, effectively increasing enzymatic activity 10-fold. The anti-PAD3/PAD4 cross-reactive antibody further stabilizes PAD4 enzymatic activity, resulting in a 400-fold increase of histone citrullination at low calcium concentrations (148). Both anti-PAD4 and anti-PAD3/PAD4 are associated with more erosive arthritis, with the severity of joint erosion observed to correlate with PAD4 activity, suggesting that these autoantibodies may accelerate RA (148).

### Mechanisms of antibody-independent arthritis

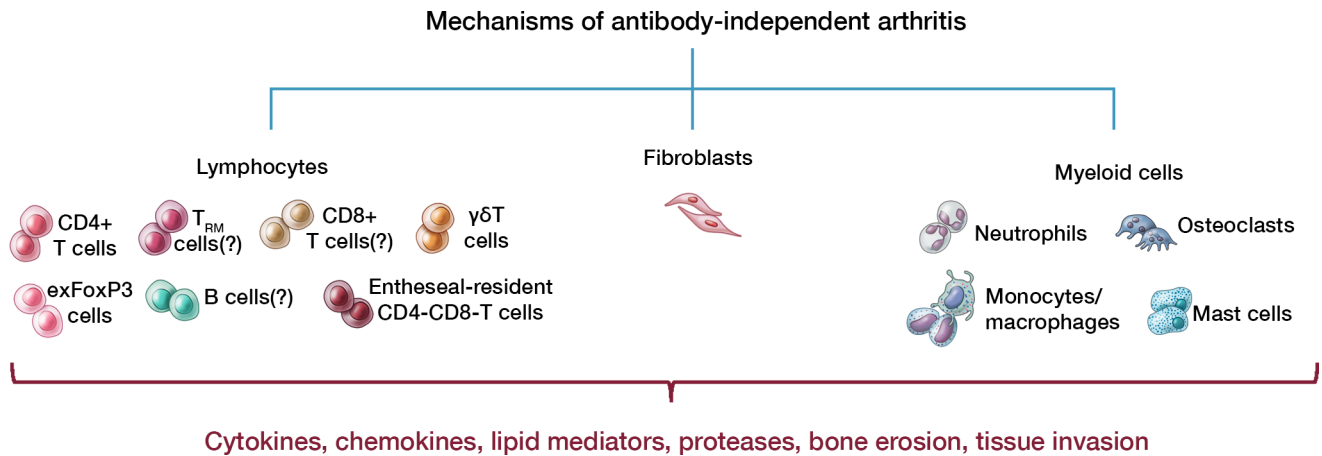
IgG is not the only pathway to inflammatory arthritis. Many patients lack any detectable arthritis-associated autoantibodies, and evidence for IgG-mediated inflammation in the joints is common but not uniform. In particular, fixation of complement is a feature of seropositive RA but is largely absent in seronegative RA, psoriatic arthritis, and reactive arthritis (64, 65, 67, 149–152). Neutrophils containing IgG ICs are observed almost exclusively in seropositive disease (66). The presence of ICs in surgically excised arthritic joint tissues is not ubiquitous but rather correlates strikingly with seropositivity (Table 2). Circulating ICs are more prevalent in seropositive disease, though methodologic challenges render this finding less clear-cut than in synovial fluid (153, 154). These studies may fail to detect arthritis induced by IgG independent of ICs but are consistent with the supposition that a sizable minority of human inflammatory arthritis arises independently of autoantibodies, a suggestion further supported by the observation that B cell-fostering T<sub>PH</sub> cells are found in much greater abundance in synovium from seropositive than seronegative patients (44).

Animal studies confirm that arthritis can arise independent of immunoglobulins (Figure 1). For example, arthritis may be engendered by an excess of TNF induced by overexpression or by mRNA dysregulation, reflecting engagement of pathogenic effector pathways without requirement for an inciting immune trigger (155, 156). Arthritis can be mediated directly by pathogenic T cells. Examples include SKG (Sakaguchi, after its discoverers) arthritis resulting from mutation in *Zap70* and arthritis due to deficiency of IL-1 receptor antagonist (*IL-1ra*), discussed further below (157, 158). In all these systems, IgG-independent arthritis clinically resembles IgG-dependent arthritis, illustrating how phenotype represents an imperfect guide to pathophysiology.

Compared with IgG-dependent arthritis (Figure 2), antibody-independent arthritis is technically more difficult to explore experimentally, but several pathways to disease have been dissected mechanistically in the mouse (Figures 1 and 3).

*CD4<sup>+</sup> T cells.* In SKG arthritis, a point mutation in the T cell receptor–signaling molecule *Zap70* leads to failure of thymic negative selection and escape of autoreactive T cells (157). Like human patients with RA, these mice express RF and other RA-associated autoantibodies and develop erosive arthritis and lung inflammation. Despite the presence of RF, disease is transferable by *CD4<sup>+</sup>* T cells rather than serum. Transfer of SKG thymocytes, but not T cell–depleted bone marrow, into T and B cell–deficient mice is sufficient to engender arthritis, excluding an obligate role for IgG (157). *CD4<sup>+</sup>* T cells directly infiltrate into the synovium, where joint inflammation is mediated by TNF- $\alpha$ , IL-1, and IL-6, reminiscent of RA (157, 159).

*$\gamma\delta$  T cells.* A second example of IgG-independent joint inflammation results from deficiency of *IL-1ra* (158). Despite the hallmark role of IL-1 in innate immunity, arthritis in mice lacking this endogenous antagonist for both IL-1 $\alpha$  and IL-1 $\beta$  is strictly dependent on T cells (160). Excess IL-1 signaling promotes the development of IL-17–producing  $\gamma\delta$  T cells that mediate arthritis dependent on IL-1 $\beta$ , IL-17A, IL-6, and IL-23R (the latter 2 required for development of Th17-like  $\gamma\delta$  T cells), as well as on pathogenic *CD4<sup>+</sup>* T cells (161–163).  $\gamma\delta$  T cells are a subpopulation of T cells that express a limited diversity of T cell receptor rearrangements and exhibit a generally tendency toward autoreactivity. They have been described in the synovium and synovial fluid of RA patients, albeit expressing IFN- $\gamma$  rather



**Figure 3. Antibody-independent processes in the initiation and perpetuation of inflammatory arthritis.** Multiple cell lineages contribute to the pathogenesis of inflammatory arthritis independent of antibodies. Murine studies implicate multiple lymphocyte subtypes in specific contexts, including CD4<sup>+</sup> T cells, exFoxP3-converted Tregs, enthesal-resident T cells, and  $\gamma\delta$  T cells. CD8<sup>+</sup> T cells and B cells/plasma cells are abundant in synovium but their role is unclear. Evidence for the presence and function of synovial T<sub>RM</sub> cells is preliminary. Fibroblasts within the synovium are heterogeneous and contribute via mediator production and direct attachment and invasion, including into cartilage. Myeloid cells of multiple types participate actively in disease. Neutrophils appear essential for the normal evolution of chronic inflammatory arthritis in most contexts. Local resident macrophages, recruited monocytes, and newly differentiated macrophages are implicated both in propagation and in resolution of synovitis. Mast cells can initiate arthritis and are abundant in chronic synovitis, but their role in established arthritis is not well defined. Osteoclasts mediate bone erosion and can potentially amplify or even initiate joint inflammation. Downstream effector pathways include cytokines (e.g., TNF, IL-1, IL-6, IL-8, IL-17), chemokines such as ligands for the chemokine receptors CCR1 and CXCR2, lipid mediators such as leukotriene B<sub>4</sub>, proteases, and direct tissue injury. Illustrated by Mao Miyamoto.

than IL-17A (164). The IL-1ra-deficient mouse may mimic arthritis arising in systemic JIA and its adult equivalent, adult-onset Still's disease, which both exhibit a key role for IL-1 early in the disease course (165).

*ROR $\gamma$ t<sup>+</sup>CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>-</sup> enthesal-resident lymphocytes and exFoxP3 cells.* Murine arthritis driven by overexpression of IL-23 begins as an enthesitis, initiated through activation of IL-23R-expressing ROR $\gamma$ t<sup>+</sup>CD3<sup>+</sup>CD4<sup>+</sup>CD8<sup>-</sup> enthesal-resident lymphocytes (166). A newly discovered lymphocyte population, these cells respond to IL-23 signaling to produce inflammatory mediators. In CIA, a population of pathogenic T cells has been identified that appear to be Tregs that have converted to Th17 cells (exFoxP3 cells) (167). These cells lose their FoxP3 expression and immunosuppressive function in an arthritic environment, subsequently becoming autoreactive T cells that produce IL-17 and promote more severe arthritis. Whether these processes are replicated in human disease is unclear, although enthesitis in spondyloarthritis patients exhibits a primarily lymphocytic infiltrate (168, 169).

*T resident memory cells.* Lymphocytes resident within joint tissues may play a key role in chronic/recurrent arthritis. Studies have identified T resident memory (T<sub>RM</sub>) cells as key drivers of recurrent site-specific inflammation in skin (170–172). Inflammatory arthritis can display similar “joint-specific memory,” with the same joints flaring again and again in a pattern characteristic of each individual (173). Preliminary evidence suggests that both human and murine synovitis feature T<sub>RM</sub> cells that could nucleate joint-specific flares (174, 175).

Multiple other IgG-independent mechanisms also contribute to inflammatory arthritis (Figure 3). For example, synovial fibroblasts are key effectors of joint inflammation, and epigenetic changes affecting these cells during the course of arthritis could convert them into autonomous agents that perpetuate local disease through mediator release and tissue invasion (102, 176, 177). Generation of endogenous TLR agonists within the inflamed joint, such as heat shock proteins, high-mobility group B1 protein, hyaluronan breakdown products, citrullinated fibrinogen, RNA, and ribosomal DNA, could supply ongoing IgG-independent stimuli to macrophages and other cells within the joint (178–183). Autoinflammatory diseases, such as familial Mediterranean fever, Blau syndrome, and PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne), feature transient or persistent arthritis that is thought to occur without adaptive immune involvement via innate lineages, such as neutrophils and macrophages. Even in arthritis triggered initially by IgG, such antibody-independent mechanisms likely contribute to the persistence of inflammation.



## Summary and synthesis

Inflammatory arthritis is a pathogenically complex disease. Disease can arise through either antibody-dependent or antibody-independent pathways (Figures 2 and 3). Long-standing arthritis can engage additional mechanisms, including antibody-independent pathways of disease perpetuation, even in disease originally sparked by autoantibodies.

Correspondingly, studies in murine models should be understood as testing specific mechanisms within arthritis, rather than arthritis biology in its entirety. This caveat is particularly important for models mediated by autoantibody transfer, which are experimentally highly tractable but cannot be expected to mirror all aspects of chronic long-standing RA. Mice and humans differ immunologically in important respects, including Fc receptor biology and IgG Fc glycosylation. A nuanced approach to animal data will restrain overly optimistic extrapolation to human disease while avoiding paralyzing skepticism about experimental models, which still represent an irreplaceable tool to interrogate disease pathogenesis in vivo.

Each mechanism outlined here represents a disease target. For autoimmune arthritis, whether mediated through antibodies or other routes, restoration of immune tolerance remains the “holy grail.” Short of this goal, numerous links in the pathogenic chain are susceptible to intervention, including antigen presentation, antibody generation, IgG antigen-binding domain and Fc glycosylation, and cytokines and cellular actors that mediate inflammation and tissue injury. Relevant targets will vary with disease category and chronicity. Divergent and partial treatment responses likely reflect the failure to address all active pathways. In aspiring to understand arthritis mechanisms better, we seek the ability to provide more specific and effective interventions and thereby attain superior clinical outcomes.

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