The Role of Antibodies in Mouse Models of Rheumatoid Arthritis, and Relevance to Human Disease

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I. Rheumatoid Arthritis: Clinical and Pathological Features

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting approximately 1% of the world's population (Lee and Weinblatt, 2001). Although inflammatory lesions in the skin, lungs, and other organs are common, the disease hallmark is severe, often destructive, inflammation of peripheral joints.

Although manifestations vary among patients, RA is usually a symmetric polyarthritis affecting distal [metacarpophalangeal (MCP), metatarsophalangeal (MTP), proximal interphalangeal (PIP), wrist, and ankle] more than intermediate (knee, elbow) and more than proximal (hip, shoulder) joints, and sparing the distal interphalangeal (DIP) joints. The cervical spine is often affected, but not the remainder of the axial skeleton. Synovial tendon sheaths and bursae are frequently involved.

Microscopically, the characteristic lesion of RA is a novel tissue called pannus, composed of a greatly expanded number of both type 1 (macrophage-like) and type 2 (fibroblast-like) synoviocytes, as well as new blood vessels and a mononuclear cell infiltrate that is often follicular and can contain germinal centers. Although neutrophils are the predominant cell in inflamed synovial fluid, they are sparse in pannus. Pannus overgrows and erodes articular cartilage; destroys bone, especially at the junction of bone and cartilage; and erodes through tendons and ligaments. Together, these processes often destroy joint function, usually over the course of many years.

II. RA: Theories of Pathogenesis

Broadly speaking, RA has been conceived of as fundamentally an autoimmune, infectious, or neoplastic disease. The pathogenesis has not been established despite considerable advances in understanding made through genetics, cell biology, and biochemistry, summarized as follows.

A. MHC AND T CELLS

Genetic linkage studies have identified the major histocompatibility complex (MHC) class II gene DR as the locus most closely associated with RA (Jawaheer *et al.*, 2003; Stasny, 1978). These findings strongly implicate CD4^{+}

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T cells somehow in pathogenesis, but do nothing to differentiate between immunity to self versus a pathogen, nor among potential downstream effector mechanisms. T cells are found in large numbers in RA lesions. Efforts to identify skewed T cell receptor (TCR) usage suggestive of clonal expansion have been inconclusive (Jenkins *et al.*, 1993; Uematsu *et al.*, 1991): attempts to identify antigenic peptides have also been unsuccessful. T cell-depleting therapies with anti-CD4 or anti-CD152 (CAMPATH-1 h) have been only transiently effective (Matteson *et al.*, 1995; Moreland *et al.*, 1995; van der Lubbe *et al.*, 1995; Weinblatt *et al.*, 1995), but depletion within the lesions was poor or transient (Ruderman *et al.*, 1995), so these trials do not really shed much light on the role of T cells in disease progression.

B. Immune Complexes and Autoantibodies

Complexes containing immunoglobulin (Ig) and the C3 component of complement are present in the synovium and articular cartilage of rheumatoid lesions (Cooke *et al.*, 1975; Vetto *et al.*, 1990) and within infiltrating phagocytes (Britton and Schur, 1971). Hemolytic complement is depleted in the synovial fluid of RA patients, in contrast to individuals with other varieties of inflammatory arthritis (Pekin and Zvaifler, 1964; Ruddy *et al.*, 1969); breakdown products of C3 provide further evidence of local complement activation in the RA joint (Mollnes *et al.*, 1986; Olmez *et al.*, 1991). Various autoantibodies are found at higher levels in RA sera than in control sera (Morgan *et al.*, 1987; Souto-Carneiro *et al.*, 2001; Verheijden *et al.*, 1997), but their role in disease is unclear. The most specific yet found are those recognizing peptides in which arginine has been modified to citrulline (Schellekens *et al.*, 1998; Vincent *et al.*, 1999). Support for a central role of antibodies (Ab) in RA has come recently from studies showing clinical effectiveness of the B cell-depleting (anti-CD20) monoclonal Ab (mAb) rituximab; in addition, disease has tended to recur only with the return of detectable B cells and auto-Ab (Cambridge *et al.*, 2002; Edwards *et al.*, 2002). However, it is not yet clear whether these findings reflect a role for Ab or some other B cell function.

Rheumatoid factors (RF)—Ab that bind to the Fc portion of IgG—are found in the sera of about 80% of RA patients, but are also found in association with other inflammatory diseases and in perhaps 5% of healthy people. RF can be recovered from RA lesions (Jasin, 1985), appear to be synthesized locally based on greater levels in synovial fluid relative to blood (Jones *et al.*, 1984), and can fix complement *in vitro* (Bianco *et al.*, 1974). RF in RA are present in higher concentrations, are of higher avidity, are more frequently of IgG isotypes, and have altered glycosylation relative to RF from control

patients (reviewed in Firestein, 2001). Nevertheless, their role, if any, in the pathophysiology of RA is still unclear.

C. CYTOKINES AND MACROPHAGES

Numerous cytokines and other mediators are found at elevated levels in RA lesions, including both pro- and antiinflammatory molecules. Macrophage-derived mediators are much more prevalent than those secreted by lymphocytes (reviewed in Firestein, 2001). As before, macrophage-like synoviocytes are a prominent feature of pannus. The effectiveness of treatments (mAb, soluble receptors, and natural receptor antagonists) that specifically block tumor necrosis factor-α (TNF-α) or interleukin (IL)-1 have confirmed the importance of these cytokines in RA (Bresnihan *et al*., 1998; Maini *et al*., 1999; Weinblatt *et al*., 1999). The usually rapid return of disease when anti-TNF treatment is discontinued shows that this treatment does little to interrupt the underlying pathophysiology, and must be interfering with a downstream effector mechanism, such as TNF production by macrophages, neutrophils, or mast cells.

D. SYNOVIAL FIBROBLASTS

Fibroblasts from RA synovium show some properties characteristic of transformed cells (reviewed in Firestein, 2001), as well as the ability to invade and destroy cartilage when cotransplanted into severe combined immunodeficient (SCID) mice (Muller-Ladner *et al*., 1996). Fibroblast-like synoviocytes can also produce some of the cytokines that are elevated in RA lesions.

E. INNATE IMMUNITY

Many of the previous elements do not strictly require the participation of the adaptive immune system in order to be activated. For this reason, and because nonspecific adjuvants can cause synovial thickening prior to or in the absence of recognizable autoimmunity, it has been proposed that RA can be explained without a role for antigen-specific immunity (Firestein and Zvaifler, 2002).

The relative importance of these components has been the subject of much debate, often unnecessarily polarized, although some authors have made an effort to promote balanced views (Panayi *et al*., 1992). Interestingly, and in our estimation for no compelling reason, the previously popular concept of RA as an immune-complex-mediated disease (Zvaifler, 1974) was discarded by all but a few (Edwards and Cambridge, 1998) theorists. Following a brief review of effector mechanisms associated with Ab and immune complexes (IC), we will summarize in the remainder of this chapter the evidence that IC produce RA-like pathology in a variety of mouse models and that these findings may be relevant to the human disease.

III. Effector Mechanisms of Antibody-Mediated Disease

A. COMPLEMENT

As reviewed in more detail by Walport (2001), the complement cascade is activated by three major means: the classical, alternative, and mannose-binding-lectin (MBL) pathways (Fig. 1). The classical pathway is activated by the Fc portions of certain isotypes of Ig if present in sufficient density to cross-link the components of C1. The alternative pathway is activated by foreign surfaces (i.e., those lacking the complement inhibitors present on host cells) and also plays an important role in amplifying the cascade initiated via other pathways. The MBL pathway is activated by terminal mannose residues found on various bacteria, and also by agalactosyl IgG, a form that is, interestingly, often found in rheumatoid joints (Malhotra *et al.*, 1995). All pathways cleave C3 and initiate the effector functions of complement. The subsequent cleavage of C5 leads to the formation of the pore-forming membrane attack complex (MAC). The released fragments C3a and especially C5a promote inflammation by binding receptors on a variety of cell types. The surface-bound or IC-bound
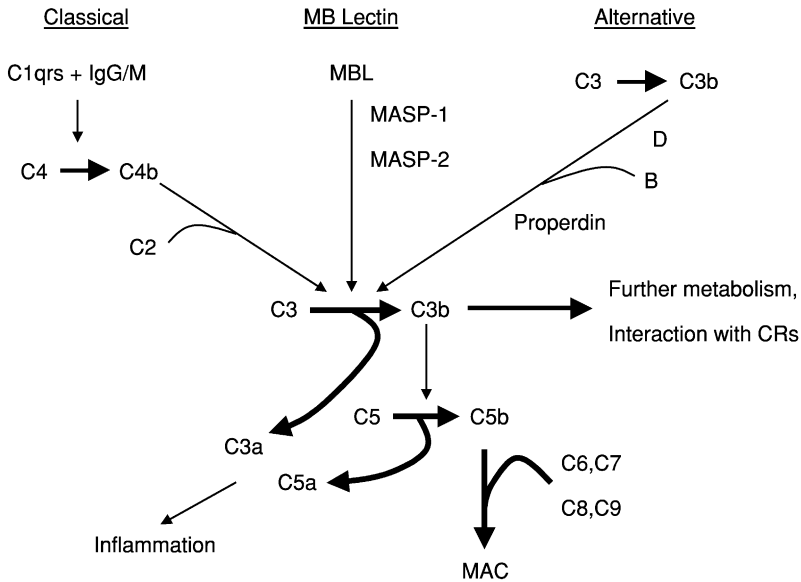

FIG 1   Outline of the complement cascade. Thick arrows denote transitions from one protein or complex into another. Thin arrows denote catalysis of such transitions by the products at the origins of the arrows. Note that the mechanism(s) by which mannose-binding lectin (MBL) can activate C3 are not fully known. MAC, membrane attack complex.

fragments of C3 interact with different cell-surface receptors (CR1, CR2, CR3) to effect phagocytosis, clearance of ICs, and immunoregulation.

B. Fc Receptors

As reviewed by Takai (2002), the Fc portions of IgG isotypes interact with multiple cell types via different cell-surface Fc receptors (FcR). Mice have three known FcR. All three types are found on macrophages, neutrophils, eosinophils, and dendritic cells, with further differences in expression as follows. FcγRI is of relatively high affinity and is also found on monocytes. FcγRII and FcγRIII are of lower affinity and therefore bind better to larger complexes with multivalent ligands. FcγRII is also found on mast cells and B cells; FcγRIII is found on monocytes, mast cells, and NK cells (reviewed in Takai, 2002). FcγRI and FcγRIII both use a common chain (FcRγ) that delivers an activating signal; FcγRII, in contrast, delivers an inhibitory signal. Human FcR are analogous but more diverse: FcγRIA, B, and C; FcγRIIA, B, and C, of which only B is inhibitory; and FcγRIIIA and B, where B has only extracellular domains attached to the plasma membrane by a GPI tail (reviewed in Takai, 2002).

C. Cells of the Innate Immune System

Neutrophils are bone-marrow-derived cells that circulate in the blood and exit into tissues at sites of incipient inflammation. Various adhesion molecules and chemotactic factors are involved in the multistep exodus (rolling, adhesion, transmigration) of these cells from the bloodstream. As reviewed by Burg and Pillinger (2001), most of the functions of neutrophils can be teleologically associated with defense against bacterial infection (phagocytosis, production of toxic oxygen radicals and bacteriocidal peptides, and secretion of proinflammatory mediators), but their products also contribute to tissue damage in both infectious and noninfectious inflammation.

Mast cells (reviewed in Gurish and Austen, 2001) are also bone-marrow-derived cells, but they circulate as committed progenitors and mature only within peripheral tissues. The phenotypic diversity of these cells appears to go well beyond the traditional subtypes of mucosal and connective tissue mast cells, but is only beginning to be described. Mast cells promote vascular permeability and influx and activation of inflammatory cells by secretion of histamine, serotonin, prostaglandins, leukotrienes, cytokines, chemokines, proteases, and proteoglycans. Mast cells are readily activated by cross-linking of the high-affinity receptor for IgE (FcεR) and are best known for their prominent role in allergy and anaphylaxis. However, interest in these cells has broadened recently with the demonstration of their importance in several animal models of non–IgE-mediated autoimmune disease (reviewed in Benoist and Mathis, 2002).

Macrophages are derived from circulating monocytes and exist in peripheral tissues in two general forms: (1) tissue macrophages, which populate normal tissues to varying degrees and can have quite specialized functions (such as osteoclasts in bone, Kuppfer cells in liver, type 1 synoviocytes in joint, microglia in brain, and alveolar macrophages in lung), and (2) inflammatory macrophages, which invade inflamed tissues, generally after neutrophils do. Macrophages are phagocytes and produce oxygen radicals, but they are involved in much more complex functions than neutrophils, including antigen presentation to T cells, removal of debris, tissue remodeling, and modulation of immune responses through the secretion of numerous cytokines and other mediators. The production of TNF and IL-1 by macrophages has been of particular interest to those studying their role in RA (reviewed in Kinne *et al.*, 2000).

IV. Animal Models: General Considerations

The major models discussed as follows have several features that differ from human RA. They are dependent upon either deliberate immunization or transgenic manipulation. Yet susceptibility to RA clearly has a genetic component and, furthermore, might be initiated by inadvertent exposure to a pathogen. Joint destruction proceeds more rapidly in animal models, over weeks rather than months to years. However, it is plausible that animal models represent more overt expression of mechanisms that occur with more subtlety in RA. Patterns of joints involvement can differ. However, the mechanical stresses on joints in bipeds and quadripeds differ, there is great heterogeneity in joint involvement even within the human disease, and distal peripheral joints tend to be affected more than proximal joints in both RA and numerous animal models. Finally, only a few models feature detectable RF. Yet, as discussed previously and later, the role of RF in RA is unclear, and in both RA and those models in which RF is found, the levels correlate imperfectly with the presence or severity of disease.

Animal models were developed in rabbits and rats before mice. The availability of numerous genetically-modified mouse strains, more extensive genetic information, and tools with which to evaluate immune responses has allowed mouse models to be explored in greater detail. The remainder of this chapter will focus on mouse models of RA, especially on elements that have been tested in multiple models, and on inflammation rather than the destruction of cartilage and bone. Special attention will be paid to those models in which the effector phase can be evaluated separately by adoptive transfer; recent studies in these models have helped produce a resurgence of interest in considering RA as a disease mediated by auto-Ab (Firestein, 2003). We will first discuss those models in which arthritis is induced by immunization, then those in which it occurs spontaneously in mutant or engineered strains.

V. Collagen-Induced Arthritis

Originally developed in rats (Trentham *et al.*, 1977) and soon after in mice (Courtenay *et al.*, 1980), collagen-induced arthritis (CIA) is produced by immunizing animals with xenogeneic type II (cartilage-specific) collagen in complete Freund's adjuvant (CFA).

In susceptible mouse strains, the most commonly used of which is DBA/1, arthritis appears in the majority of mice 3–5 weeks after immunization (Courtenay *et al.*, 1980). Often a booster immunization in incomplete adjuvant (IFA), CFA or saline is used but is not strictly required. Disease primarily affects the front and rear paws, with occasional involvement of the spinal column, tail, and ear (Courtenay *et al.*, 1980). Investigators generally examine the tarsal joints histologically, and we are not aware of a study documenting the degree of inflammation in proximal versus distal joints. Histologically, synovial hyperplasia is a relatively early finding, followed by infiltration of the synovium, subsynovial connective tissue, and joint space with neutrophils, then mononuclear cells. Subsequently, pannus develops, with erosion of cartilage and bone (Courtenay *et al.*, 1980). IgG and C3 accumulate on the cartilage surface, but not in the synovium (Wang *et al.*, 2000).

Susceptibility to CIA in mice is linked to the MHC class II region (Wooley *et al.*, 1981). CD4$^+$ T cells (Ranges *et al.*, 1985) and B cells (Svensson *et al.*, 1998) are required for the full spectrum of disease, although DBA/1 mice deficient in the RAG1 gene (and thus lacking mature B and T lymphocytes) still develop some synovial hyperplasia, pannus, and erosion of cartilage and bone (Plows *et al.*, 1999). Depletion of macrophage-like synoviocytes by local injection of clodronate-containing liposomes decreases inflammation (van Lent *et al.*, 1996) and cartilage loss (van Lent *et al.*, 1998b).

Various cytokines are important in CIA. Blockade of TNF-α markedly decreases inflammation and joint destruction when given early (Williams *et al.*, 1992), but its effectiveness in established disease has been less clear (Joosten *et al.*, 1996). Blockade of IL-1 also prevents arthritis and is particularly protective against destruction of cartilage and bone (Joosten *et al.*, 1996, 1999). Mice lacking IL-6 are resistant to CIA (Alonzi *et al.*, 1998), and blockade of IL-18 reduces disease (Plater-Zyberk *et al.*, 2001). Mice lacking IL-10 develop more severe arthritis (Cuzzocrea *et al.*, 2001), and exogenous IL-10 ameliorates disease (Joosten *et al.*, 1997a). The roles of IL-4 and IL-12 are complex, apparently different in different phases of disease (Joosten *et al.*, 1997b; Svensson *et al.*, 2002).

Susceptible strains generate Ab binding to both the immunizing (xenogeneic) and autologous type II collagen. In support of these Ab playing an important role in disease, mice deficient in C3 (Hietala *et al.*, 2002), factor B (Hietala *et al.*, 2002), or C5 (Wang *et al.*, 2000) are resistant to CIA, and

anti-C5 mAb prevents CIA and ameliorates established disease (Wang *et al.*, 1995). Mice lacking the shared FcRγ chain (therefore lacking FcγRI, FcγRIII, and FcεR) (Kleinau *et al.*, 2000) or only FcγRIII (Diaz *et al.*, 2002) are highly resistant to CIA, whereas mice lacking the inhibitory receptor FcγRII develop more severe disease (Kleinau *et al.*, 2000). Most importantly, arthritis can be transferred to naïve mice using serum from arthritic mice (Stuart and Dixon, 1983), or a mixture or mAb to type II collagen (Terato *et al.*, 1992).

Arthritis produced by passive transfer of anticollagen Ab resembles actively induced CIA, but is milder, much more rapid in onset, and transient (Stuart and Dixon, 1983). Disease is evident 2–3 days after an injection of Ab, is maximal a day later, and gradually resolves over the next 4–5 days. Deposits of IgG and C3 are found, as in the case of active immunization (Stuart and Dixon, 1983). Disease susceptibility is independent of MHC alleles (Stuart and Dixon, 1983), and T and B cells are dispensable (Kagari *et al.*, 2002). IL-1 and TNF-α are required, but IL-6 is not (Kagari *et al.*, 2002). C5 (Watson *et al.*, 1987) and the C5aR (Grant *et al.*, 2002) are required in recipient mice; such mice still accumulate IgG and C3 on the articular surface, but without inflammation. Mice lacking the common FcRγ chain are highly resistant and those lacking FcγRIII partially so. Absence of FcγRII does not appear to exacerbate disease (Kagari *et al.*, 2003).

Thus the ability to isolate the effector phase has allowed a more precise assignment of roles for complement and cytokines in CIA, although these findings do not preclude roles for these factors in the induction phase. Likewise, an Ab-independent role for T cells in the effector phase is not precluded, but supporting data are lacking.

VI. Antigen-Induced Arthritis

Originally described in rabbits (Cooke *et al.*, 1972) and later in mice, (Brackertz *et al.*, 1977a), antigen (Ag)-induced arthritis (AIA) is produced by immunizing an animal systemically with an Ag and challenging locally, typically 21 days later, with the same Ag in a knee joint. Since inflammation is confined to the injected joint, AIA is not precisely a model of RA, but it is plausible that the principles operating in this model could apply to a symmetric polyarthritis in which the target Ag resides in multiple joints.

Methylated bovine serum albumin (mBSA) has been the most frequently used Ag, although others have been employed. Cationic Ags work better than neutral or anionic ones, correlating with the greater retention of cationic proteins in articular cartilage (van den Berg *et al.* 1984; van den Berg and Van de Putte, 1985). Histopathologically, affected joints develop mixed inflammatory infiltrates (predominantly mononuclear cells, with neutrophils in synovial effusions), synovial hyperplasia, pannus, and destruction of cartilage and

bone; a smoldering synovitis persists for at least 3 months (Brackertz *et al.*, 1977a). Ab, Ag, and C3 are colocalized on the articular surface (Cooke *et al.*, 1972; van den Berg and Van de Putte, 1985). Not all mouse strains are susceptible (Brackertz *et al.*, 1977a), but linkage to the MHC has not been described. T cells are required, based on the absence of disease in athymic nude mice (Brackertz *et al.*, 1977a). T cells from immunized mice can transfer disease susceptibility to naïve mice (Brackertz *et al.*, 1977b), but no results in B cell-deficient mice have been reported. Antiserum has been reported to cause only mild synovial hyperplasia and mononuclear cell infiltration of subsynovial connective tissue (Brackertz *et al.*, 1977b). Mast cells are not required for inflammation, but may promote cartilage destruction (van den Broek *et al.*, 1988). In a modification of AIA, in which an intravenous injection of Ag causes acute reactivation of chronic disease locally, depletion of local macrophage-like synoviocytes with clodronate-impregnated liposomes markedly decreases disease (van Lent *et al.*, 1998a). In this same "flare-up" model, depletion of complement with cobra venom factor has no effect (Lens *et al.*, 1984).

Blockade of either IL-1, TNF-α, or IL-6 has no effect on acute inflammation in AIA, although IL-1 blockade markedly reduces chronic inflammation (van de Loo *et al.*, 1995). The common FcRγ chain is important in acute and chronic inflammation (van Lent *et al.*, 2000), but the absence of FcγRI or FcγRIII individually has little effect (van Lent *et al.*, 2001); FcγRI is important, however, in destruction of cartilage (van Lent *et al.*, 2001). Disease is more severe in mice lacking FcγRII (van Lent *et al.*, 2001).

Thus there is only indirect evidence for an important role for Ab in AIA, and no evidence for such in the flare-up reaction. However, a similar disease can be induced by injection of a different cationic Ag, lysozyme-poly-L-lysine, into the knees of mice passively immunized with Ag-specific rabbit Ab (van Lent *et al.*, 1992). Arthritis, featuring a massive influx of neutrophils, is evident within 1 day and wanes over the course of a week (van Lent *et al.*, 1992). Ag is deposited on the articular surface, presumably in complex with specific Ab (van Lent *et al.*, 1992). Local depletion of macrophage-like synoviocytes prevents disease (van Lent *et al.*, 1993), as in the flare-up reaction of active AIA. No role for T or B cells has been reported; such would be unlikely in light of the rapidity of the response. IL-1 is required for inflammation and cartilage destruction (van Lent *et al.*, 1992, 1995), but TNF-α may be dispensable (van Lent *et al.*, 1995). FcγRIII is required for inflammation and cartilage breakdown, whereas FcγRI seems to be important only in cartilage loss (Nabbe *et al.*, 2003). FcγRII plays a suppressive role, since inflammation and cartilage breakdown are enhanced in FcγRII-deficient mice (Nabbe *et al.*, 2003). The complement system is also required for disease, since treatment with cobra venom factor largely prevents arthritis (van Lent *et al.*, 1992); the roles of individual components have not been reported.

VII. Proteoglycan-Induced Arthritis

BALB/c mice immunized with human fetal cartilage proteoglycan (PG) in CFA uniformly develop arthritis of gradual onset (Glant *et al.*, 1987). Redness and some swelling are noted as early as 9–12 days postinjection. Swelling is maximal at 7–9 weeks, usually affects all four paws, and progresses to joint destruction. Distal joints, knees, elbows, lumbar spine, and tail are affected (Glant *et al.*, 1987). Histologically, synovium, subsynovial connective tissue, and other periarticular tissue are infiltrated by mononuclear cells and, to a lesser extent, neutrophils, beginning in perivascular areas. Pannus forms and erodes cartilage and bone, with progression to ankylosis (Glant *et al.*, 1987). Ig is deposited in the synovium and articular cartilage (Mikecz *et al.*, 1987).

Proteoglycan-induced arthritis (PGIA) has been found only in BALB/c mice, although other strains, including those of the same MHC haplotype, can make T cell and Ab responses to PG (Mikecz *et al.*, 1987). Based on studies with subset-depleting mAb, $CD4^+$ cells are required, but $CD8^+$ cells are not (Banerjee, *et al.*, 1992). PGIA can be transferred to irradiated BALB/c mice using restimulated lymphocytes; both T and B cells are needed (Mikecz *et al.*, 1990). B cell-deficient mice, as well as mice with B cells bearing surface IgM but unable to secrete Ig, are completely resistant (O'Neill *et al.*, 2001). Development of PGIA is preceded by production of Ab binding both the xenogeneic and autologous PG, and many immunized mice produce RF (Mikecz *et al.*, 1987), but disease has not been transferred with antiserum (Mikecz *et al.*, 1990).

PGIA is more severe in IL-4-deficient and less severe in IFNγ-deficient mice (Kaplan *et al.*, 2002a). The roles of TNF-α, IL-1, and complement have not yet been reported. Mice lacking FcRγ (and therefore both FcγRI and FcγRIII) are completely resistant, despite producing effective immunity, as shown by the ability of cells from such mice to cause disease upon transfer into $FcR\gamma^+$ but lymphocyte-deficient SCID mice (Kaplan *et al.*, 2002b). Mice lacking FcγRII develop more severe PGIA (Kaplan *et al.*, 2002b).

Thus, although PGIA has not been transferred to naïve mice using Ab, there is considerable indirect evidence that it is an Ab-mediated disease.

VIII. Streptococcal Cell Wall Arthritis

Rats given a single intraperitoneal (i.p.) injection of a sonicate of streptococcal cell walls (SCW) develop progressive polyarthritis shortly thereafter (Cromartie *et al.*, 1977). Mice do not produce such a response, but have been reported to develop a transient polyarthritis (Koga *et al.*, 1985). SCW have been used to induce murine arthritis in two other ways (reviewed in Joosten *et al.*, 2000a). First, in a manner analogous to AIA, mice immunized

systemically with SCW develop chronic, destructive arthritis in a knee joint after intraarticular injection of SCW. Second, injection of SCW into the knee joints of naïve mice produces an acute, transient arthritis. In the latter model, neutrophil influx is apparent on Day 1 and is maximal between Days 2 and 4; macrophage infiltration is evident on Days 4–7, and inflammation subsides thereafter. PG is depleted from cartilage. According to the timing of the response, acute SCW arthritis is thought not to involve the adaptive immune system. Based on blockade of cytokines with mAb, TNF-α plays an important role in joint swelling, and IL-1 is important in both inflammation and cartilage destruction (Kuiper *et al.*, 1998). Blockade of IL-18 suppresses swelling, inflammation, and cartilage loss (Joosten *et al.*, 2000b). IL-4 and IL-10 appear to play protective roles (Lubberts *et al.*, 1998).

IX. Pristane-Induced Arthritis

Injection of the hydrocarbon pristane (2,6,10,14-tetramethylpentodecane) i.p. into mice of susceptible strains leads to chronic arthritis, with an incidence of 22–100%, beginning 2–10 months after injection (Potter and Wax, 1981; Wooley *et al.*, 1989). Ankles and wrists are most prominently affected (Wooley *et al.*, 1989). The histological picture is dominated by mononuclear cell infiltration, later forming pannus with erosion of cartilage and bone. Nodules are found with central necrosis and surrounding macrophages, analogous to rheumatoid nodules (Wooley *et al.*, 1989). A similar disease occurs in rats.

The role of MHC and other genes is unclear (Wooley *et al.*, 1989). T cells are involved, based on resistance of athymic nude mice (Wooley *et al.*, 1989). Depletion of CD4$^+$ cells with mAb decreases severity of disease (Levitt *et al.*, 1992). Susceptibility can be reconstituted in sublethally irradiated mice using CD4$^+$ cells in the absence of CD8$^+$ or B cells (Stasiuk *et al.*, 1997). Mice treated with pristane develop anti-type-II-collagen and IgM RF auto-Ab, but there is only a modest correlation between disease and titer of either of these Ab (Wooley *et al.*, 1989). Two different C5-deficient strains are resistant to disease (Wooley *et al.*, 1989). Anti-TNF treatment reduces incidence and severity (Beech and Thompson, 1997).

X. Zymosan-Induced Arthritis

Zymosan, a glycan derived from yeast cell walls, activates complement by the alternative pathway and produces inflammatory arthritis within 48 h of intraarticular injection in mice (Keystone *et al.*, 1977). The arthritis resolves over about 2 weeks. An infiltration of neutrophils is seen first, followed by synovial hyperplasia and macrophage infiltration, with pannus formation (Keystone *et al.*, 1977). Neutralization of IL-1 or TNF-α has only modest

effects on inflammation (van de Loo *et al.*, 1995), although mice lacking these cytokines by gene disruption have not been tested.

XI. Adjuvant Arthritis

Adjuvant arthritis (AA) is a disease produced in rats by immunization with killed *Mycobacterium tuberculosis*. This disease has been difficult to recapitulate in mice (Knight *et al.*, 1992; Yoshino *et al.*, 1998).

XII. K/BxN (Anti-GPI-Mediated) Arthritis

The K/BxN (or KRN or anti-GPI) model of RA was discovered fortuitously when a mouse bearing transgenes encoding the KRN TCR (reactive with bovine RNase presented by A^k) was bred to an NOD mouse (Kouskoff *et al.*, 1996). Subsequent studies have revealed that the disease is caused by T and B cell autoimmunity to the glycolytic enzyme glucose-6-phosphate isomerase (GPI).

Mice expressing the KRN TCR and the MHC class II allele A^{g7} (K/BxN) invariably and spontaneously develop severe peripheral arthritis beginning at about 3 weeks of age. Distal joints, including tarsal, carpal, and all IP joints, are severely affected; knees and elbows are involved but less severely; hips, shoulders, and spine are spared (Kouskoff *et al.*, 1996). Histologically, a mixed infiltrate of neutrophils and mononuclear cells is seen in the synovium and subsynovium, with neutrophils predominant in the joint space. The mononuclear infiltrate becomes more prominent over time, develops into pannus, and erodes cartilage and bone; joint damage progresses to ankylosis (Kouskoff *et al.*, 1996).

Development of disease is dependent on the MHC molecule A^{g7}, but independent of other genes from the autoimmunity-prone NOD background (Kouskoff *et al.*, 1996). $CD4^+$ T cells and B cells are required (Korganow *et al.*, 1999). Blockade of TNF-α with mAb (starting at 3 weeks of age) does not prevent disease (Kyburz *et al.*, 2000), although the role of this cytokine in K/BxN mice has not been tested more definitively in TNF knockout mice. Most importantly, disease can be transferred to naïve mice using 100–300 μl of K/BxN serum (Korganow *et al.*, 1999). This serum contains large amounts (>10 mg/ml) of Ab recognizing GPI (Matsumoto *et al.*, 1999); affinity-purified anti-GPI Ab (Matsumoto *et al.*, 1999) or a combination of two or more anti-GPI mAb (Maccioni *et al.*, 2002) can cause arthritis. The KRN TCR recognizes a peptide derived from GPI, in the context of A^{g7} (Matsumoto *et al.*, 1999). Only one finding supports a role for KRN T cells in arthritis independent of B cells: a single injection of anti-GPI Ab causes prolonged and more severe arthritis in B cell-deficient ($\mu^{-/-}$) K/BxN mice, whereas the arthritis

is transient in nontransgenic mice (Korganow *et al.*, 1999). However, the basis for this apparent difference remains to be explored.

The arthritis produced by transfer of anti-GPI serum affects the carpal and tarsal joints predominantly; the MCP, MTP, IP, knee, and elbow variably; and spares the hip, shoulder, and spine (Korganow *et al.*, 1999). Arthritis is clinically apparent 1–4 days after injection, peaks at 10–14 days, and resolves slowly over the next 2 weeks. Severe arthritis is maintained if repeated injections of serum are given (Korganow *et al.*, 1999). Histologically, degranulation of mast cells is apparent within an hour (Lee *et al.*, 2002a), and influx of neutrophils is prominent within 1–2 days (Wipke and Allen, 2001); synovial hyperplasia and mononuclear cell infiltration, with pannus formation and erosion of bone and cartilage, begin within a week (Korganow *et al.*, 1999; Wipke and Allen, 2001). Affected joints have colocalizing deposits of Ig, Ag, and C3 (Matsumoto *et al.*, 2002).

Arthritis caused by Ab transfer is independent of MHC haplotype and occurs readily in RAG1$^{-/-}$ mice, which lack mature T and B cells (Korganow *et al.*, 1999). Mice lacking neutrophils (by treatment with anti-Gr-1 Ab) are resistant (Wipke and Allen, 2001); those lacking macrophage-like synoviocytes (*op/op* mice) are susceptible (Bruhns *et al.*, 2003; Lee *et al.*, 2002b). Mice lacking c-kit or its ligand, and therefore profoundly deficient in mast cells, are resistant, and susceptibility can be restored by reconstitution with mast cell precursors (Corr and Crain, 2002; Lee *et al.*, 2002a).

Disease caused by serum transfer is diminished in mice lacking TNF-α and absent in mice lacking IL-1R1 (Ji *et al.*, 2002b). IL-4 (Ohmura *et al.*, 2002) and IL-6 (Ji *et al.*, 2002b) are dispensable. The roles of complement components have been evaluated in detail (see Fig. 1 for a diagram of the cascade) using gene-disrupted or congenic strains: factor B, C3, and C5 are required, whereas C1q, C4, MBL-1, and C6 are not (Ji *et al.*, 2002a). The C5aR is required, but CR1, 2, and 3 are not (Ji *et al.*, 2002a; Solomon *et al.*, 2002). Thus the critical role of complement seems to be activation through the alternative pathway leading to the generation of C5a. In contrast to CIA, nonarthritic mice lacking C5 do not have deposits of Ab, Ag, and C3 on the articular surface (Ji *et al.*, 2002a).

FcγRIII-deficient mice are resistant, whereas FcγRI-deficient mice are susceptible; mice lacking the common chain FcRγ were reported to be more resistant than those lacking only FcγRIII (Ji *et al.*, 2002a), although an independent strain with disruption of FcgRIII appears to be completely resistant (J. Ravetch, personal communication). In our laboratory, absence of FcγRII had no effect (Ji *et al.*, 2002a), but others have found an earlier onset and/or greater severity of disease in such mice (Corr and Crain, 2002). The "neonatal," MHC-like FcR (FcRn) is also required for Ab-transferred disease; resistance is associated with a very short circulating half-life of the

transferred Ab, with the site of clearance uncertain (D. Roopenian, personal communication).

XIII. Arthritis in the lpr Mouse

The MRL/lpr mouse gets a disease very similar to human systemic lupus, as well as a lymphoproliferative disorder, due to absence of the proapoptotic Fas molecule in combination with undefined gene products of the MRL background (Andrews *et al.*, 1978). Arthritis is among the common manifestations. In the first description, 75% of 5-month-old female mice had inflamed joints, and half of those had significant joint destruction (Hang *et al.*, 1982); however, the frequency and severity of arthritis seem to vary among laboratories (Gilkeson *et al.*, 1992; Hang *et al.*, 1982; Kamogawa *et al.*, 2002; O'Sullivan *et al.*, 1985).

In the initial report, synovial hyperplasia and subsynovial infiltration (mononuclear cells more than neutrophils) were noted at 3–4 months, followed by pannus formation and destruction of cartilage and bone. Subcutaneous fibrinoid nodules similar to rheumatoid nodules were noted, as well as inflammation of periarticular structures and vasculitis (Hang *et al.*, 1982). A second study, however, reported joint destruction with synovial hyperplasia, but only a modest inflammatory infiltrate (O'Sullivan *et al.*, 1985). Arthritis in the lpr mouse appears to be a complex trait influenced by multiple undefined genes (Kamogawa *et al.*, 2002).

Depletion of $CD4^+$ cells inhibits development of arthritis (Gilkeson *et al.*, 1992); there have been no reports on B cell-deficient mice. MRL/lpr mice have numerous auto-Ab of uncertain relevance to arthritis, including RF (Hang *et al.*, 1982) and Ab to collagens and other extracellular matrix proteins (Gay *et al.*, 1987; Ratkay *et al.*, 1991). In the first report, levels of IgM RF correlated well with arthritis (Hang *et al.*, 1982). Immune complexes with features of cryoglobulins (precipitating spontaneously in the cold) isolated from lpr serum cause arthritis in MRL (non-lpr) mice when injected intraarticularly; the transient inflammation can be prolonged by repeated injection (Itoh *et al.*, 1991).

Arthritis in lpr mice can be enhanced by administration of IL-1 (Hom *et al.*, 1990) or CFA (Ratkay *et al.*, 1993). No findings have been reported for mice lacking particular cytokines, complement factors, or FcR.

XIV. HTLV Transgenic Mouse

On several genetic backgrounds, mice transgenic for the pX region of the human T cell leukemia virus type 1 (HTLV-1) develop a chronic inflammatory arthritis (Iwakura *et al.*, 1991). Incidence in susceptible strains varies from

about 30% to 70% (Iwakura *et al*., 1998; Yamamoto *et al*., 1993). The ankle is most prominently affected; the hindlimb more than the forelimb; and the shoulder, knee, and elbow more than the wrist, finger, and toe (Iwakura *et al*., 1991). Histologically, synovial proliferation is seen first, followed by formation of synovial villi, cell infiltration (neutrophilic more than mononuclear), pannus formation, destruction of cartilage and bone, formation of lymphoid follicles, and vascular changes (Yamamoto *et al*., 1993).

Genetic background is important to susceptibility, since BALB/c mice have 72% incidence and C57BL/6 mice only 2%. This difference is not due to MHC alleles, based on information from H-2 congenic strains (Iwakura *et al*., 1998). The importance of different cell types has not been reported. However, several auto-Ab are produced, including RF, anti-type-II collagen, and Abs to heat shock proteins (HSP) (Iwakura *et al*., 1995). There is also evidence for expansion of T cells specific for type II collagen, and HTLV-1 transgenic mice are highly susceptible to CIA, inviting the hypothesis that arthritis in these mice is mediated at least in part by autoimmunity to type II collagen (Kotani *et al*., 1999).

Mice lacking IL-1 are relatively resistant to arthritis in this model (Saijo *et al*., 2002). The roles of other cytokines, complement, and FcR have not been reported.

XV. Human TNF Transgenic Mouse

Mice transgenic for a modified human TNF (huTNF) gene develop a chronic inflammatory polyarthritis (Keffer *et al*., 1991). Truncation of the 3′ end of the gene leads to deregulated expression, including expression in synovium (Douni *et al*. 1995; Keffer *et al*., 1991). One hundred percent of transgenic mice are affected, beginning at 3–4 weeks of age with ankle swelling and progressing to joint destruction by 9–10 weeks. Histologically, synovial hyperplasia and mixed (neutrophilic and mononuclear) infiltrates are seen early, followed by pannus formation, destruction of cartilage and bone, and fibrosis (Keffer *et al*., 1991).

Arthritis is more severe on the DBA/1 than on the C57BL/6 × CBA background (Butler *et al*., 1997), but little else is known about susceptibility genes. Arthritis is independent of T and B cells, as it still occurs in RAG1-deficient mice (Douni *et al*., 1995). Development of arthritis is, predictably, completely blocked by anti-huTNF Ab, but it is also prevented by Ab to the murine IL-1R1; such mice also have decreased levels of circulating huTNF (Probert *et al*., 1995).

XVI. IL-1ra Knockout Mouse

Mice with targeted disruption of the IL-1 receptor antagonist (IL-1ra) on the BALB/c, but not on the C57BL/6, background invariably develop chronic inflammatory polyarthritis, primarily of the ankles (Horai *et al.*, 2000). The usual features of synovial hyperplasia, mixed inflammatory infiltration, pannus formation, and erosion of cartilage and bone are seen, starting between 5 and 8 weeks of age (Horai *et al.*, 2000). This gene deletion does not lead to arthritis in RAG2-deficient mice (Iwakura, 2002), indicating an essential role for T and/or B lymphocytes. Auto-Ab, including RF (IgG but not IgM subclass), anti–type II collagen, and anti-dsDNA, are induced, but their role is unknown (Horai *et al.*, 2000).

XVII. Mutant IL-6 Receptor Mouse

Mice engineered to have a point mutation in a phosphatase-binding site of the gp130 subunit of the IL-6 receptor develop inflammatory arthritis (Atsumi *et al.*, 2002). Lymphocytes are required for disease to occur. Thymic and peripheral T cell tolerance are impaired, and autoAb are made. No other mechanistic details are known as yet.

XVIII. Other Models

Arthritis can be produced by immunization with components of cartilage other than type II collagen or PG, namely, type IX collagen, type XI collagen (Boissier *et al.*, 1990), cartilage link protein (Zhang *et al.*, 1998), and YKL-39 (Sakata *et al.*, 2002). A transient but destructive AIA can be induced in the knees of nonimmunized mice if IL-1 is given subcutaneously concurrently (Staite *et al.*, 1990). Some inbred strains, such as DBA/1 (males only), develop spontaneous arthritis at an advanced age (Bouvet *et al.*, 1990; Nordling *et al.*, 1992). These models have not been dissected in detail; in DBA/1 males, disease is not dependent on T cells and more closely resembles ankylosing spondylitis than RA (Corthay *et al.*, 2000).

Intraarticular injection of DNA sequences containing unmethylated CpG motifs (characteristic of bacterial DNA) causes an inflammatory arthritis lasting about 14 days (Deng *et al.*, 1999). Macrophages are the dominant infiltrating cell, and neutrophils and lymphocytes appear to be dispensable (Deng *et al.*, 2000). The disease is greatly attenuated in mice lacking TNF-α (Deng *et al.*, 1999). Although this model is primarily one for septic arthritis and reactive arthritis, its findings may be relevant to RA, since the role of infection and stimulation of cells via toll-like receptors (TLRs) is unclear.

Human synovial tissue and cartilage can be transplanted into SCID mice without any apparent host reaction (Geiler *et al.*, 1994; Rendt *et al.*, 1993). Synovial tissue or isolated synovial fibroblasts from RA patients erode normal human cartilage in this model, showing an intrinsic destructive behavior of these cells independent of ongoing immunity (Geiler *et al.*, 1994; Muller-Ladner *et al.*, 1996). The model has been very useful for evaluating synovial fibroblasts and is beginning to be used for immunological studies; for example, activation of T cells requires HLA matching and cotransplanation of B cells (Takemura *et al.*, 2001).

Mouse models that resemble ankylosing spondylitis (Khare *et al.*, 1995) and psoriatic arthritis (Bardos *et al.*, 2002) have been developed. Abs have not been implicated in these models, and, notably, there is no compelling evidence for auto-Ab involvement in the human diseases they resemble.

XIX. Summary of Mouse Models

As described earlier and summarized in Table I, among those models in which numerous aspects of immune function have been evaluated, there is far more similarity than difference. A requirement for both B and CD4$^+$ T cells is prominent in models induced by active immunization or autoreactive trans-gene-encoded TCRs, but is absent in models induced by passive immunization with Ab. There is substantial agreement on the roles of different FcR, especially on the common FcRγ chain as an effector and on FcγRII as a suppressor of arthritis. The importance of TNF-α and IL-1 is more evident in passive models, perhaps because it is easier to fully block the effects of mediators in the setting of milder disease. Notably, most of the active models have not been evaluated in mice lacking cytokine or cytokine receptor genes due to gene disruption.

A general scheme for the development of arthritis in mice is proposed in Fig. 2. In most of the models discussed earlier, T cell reactivity, whether produced by intentional immunization or spontaneous loss of tolerance, leads to the production of Ab. A role for these Ab in disease is established by either the ability to transfer disease using Ab or by a dependence on FcR. The formation of IC leads to activation of complement and of various effector cells of the innate immune system (macrophages, mast cells, and neutrophils); the importance of particular cell types varies among models. These innate effector cells produce many mediators, most prominently TNF and IL-1, which provide an important positive feedback to promote further inflammation; in addition, IL-1 stimulates joint destruction.

Most models in which T and/or B cells are dispensable are, nevertheless, consistent with this pathway, initiating pathology at different points. All models in which Ab is given passively subvert the need for T cell or B cell reactivity in

TABLE I
Characteristics of Mouse Models and Human RA[a]

	Active				Passive			RA
	CIA	K/BxN	AIA	PGIA	CIA	Anti-GPI	AIA/ICA	
Deposits: Ig/C3	+	+	+	+	+	+	+	+
MHC II restriction	+	+	nr	nr	−	−	nr	+
T cells	+	+	+	+	−	−	nr	+/−
CD4+ cells	+	+	nr	+	−	−	nr	+/−
B cells	+	+	nr	+	−	−	nr	+
Macrophages	+	nr	(+)[b]	nr	nr	(−)[c]	+	nr
Neutrophils	nr	nr	nr	nr	nr	+	nr	nr
Mast cells	nr	nr	−	nr	nr	+	nr	nr
Transfer by Ab	+	+	+/−	−	(na)	(na)	(na)	−
Complement: CVF	nr	nr	(−)[a]	nr	nr	nr	+	nr
Complement: C5	+	nr	nr	nr	+	+	nr	+/−
Complement: C5aR	nr	nr	nr	nr	+	+	nr	nr
FcRγ	+	nr	+	+	+	+	+	nr
FcγRI	−	nr	−	nr	+/−	−	+/−	nr
FcγRIII	+	nr	−	nr	+	+	+	nr
FcγRII	−−	nr	−−	−−	−	−−	−−	nr
TNF-α	+(Ab)	−(Ab)	−(Ab)	nr	+(Ab)	+(KO)	−(Ab)	+
IL-1	+	nr	+/−	nr	+	+	+	+
IL-6	+	nr	−	nr	−	−	nr	+
IL-10	−−	nr	nr	nr	nr	nr	nr	nr
IL-18	+	nr	nr	nr	nr	nr	nr	nr

[a] +, required; −, not required; −−, protective; nr, not reported; na, not applicable; CVF, cobra venom factor; (Ab), anti-TNF mAb; (KO), knockout mouse.
[b] "Flare-up" reaction.
[c] Method different from others.

the host. CpG directly activates innate immune system cells, and zymosan directly activates complement. Local injection of SCW induces TNF in the joint, and the huTNF transgenic mouse produces high levels spontaneously, particularly in the joint. Only two models cannot be readily incorporated into this scheme: pristane-induced arthritis and the flare-up reaction of AIA, in which T cells are required but B cells are not.

Of course, many complex issues are touched upon only lightly in this scheme: the breaking of tolerance; the rich variety of inflammatory responses; and the means by which IL-1, TNF-α, and probably numerous other mediators contribute to joint destruction.

Models that rely on immunization involve immunity to antigens that are joint specific either innately (CIA, PGIA) or experimentally (AIA). However, in the K/BxN model, in which the factors that govern disease are similar to these
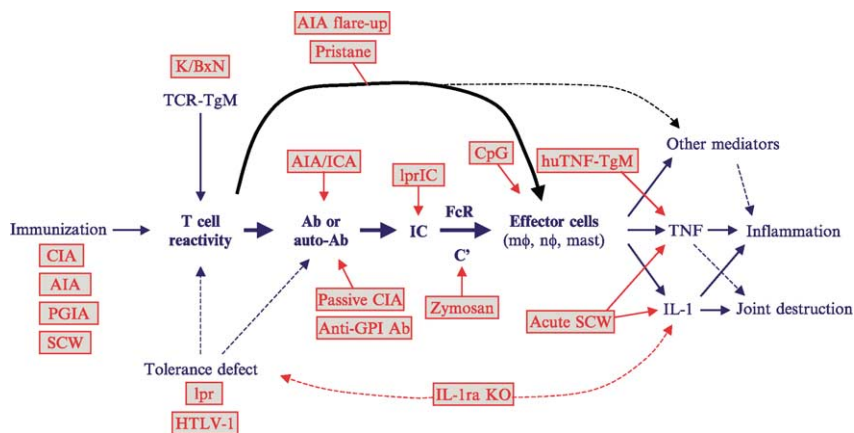
FIG 2 General mechanism for the development of inflammatory arthritis in mice. Elements of the mechanism are shown in blue, the names of various mouse models boxed in red, and Ab-independent pathways in black. Thick arrows connect the common mechanistic components. Thin arrows show diversity of mechanism at particular points, as well as the entry points of the mouse models. Dotted lines show hypothetical or less-well-documented pathways; for example, it is unclear whether loss of tolerance in the lpr and HTLV-1 models is at the level of B cells as well as T cells. "Other mediators" include angiogenic factors, arachidonic acid derivatives, cytokines, and chemokines. CIA, collagen-induced arthritis; AIA, antigen-induced arthritis; PGIA, proteogly-can-induced arthritis; SCW, staphylococcal cell wall-induced arthritis; TgM, transgenic mouse; HTLV-1, HTLV-1 transgenic mouse; IC, immune complexes; ICA, immune-complex arthritis; C, complement; anti-GPI, arthritis from passive transfer of anti-GPI Ab; IL-1ra KO, IL-1ra gene knockout on BALB/c background; CpG, arthritis from injection of hypomethylated CpG-rich DNA; mϕ, macrophages; nϕ, neutrophils; huTNF-TgM, mouse transgenic for deregulated human TNF. (See Color Insert.)

other models, immunity is directed against an Ag that is found in all cells and circulates at low levels in the blood (Matsumoto *et al*., 1999, 2002). Thus a joint-specific autoimmune disease need not involve immunity to a joint-specific Ag; it is, nevertheless, likely that the distribution of GPI in the normal joint (on the articular surface or otherwise) is important in its arthritogenic properties (Matsumoto *et al*., 2002).

Thus noting the compatibility among many mouse models, the question of how closely they resemble human RA must be addressed.

XX. Relevance to RA

The pathology and time course of RA were described at the outset of this chapter. All of the models mentioned previously have been described as having pathology that closely resembles RA. Although we cannot argue the fine points

of histopathology in the various models and in RA, it seems fair to conclude that RA-like pathology can be produced by a variety of insults. Therefore it is reasonable to propose that human RA could be integrated into the pathway shown in Fig. 2 (and described earlier) at any point. The question then arises: at which point or points?

Susceptibility to RA is more closely linked to the MHC class II locus HLA-DR than to other, as yet undefined, genes (Jawaheer *et al.*, 2003; Stasny, 1978). Thus $CD4^+$ cells are implicated, although their importance has not been formally demonstrated in clinical trials (Moreland *et al.*, 1995; van der Lubbe *et al.*, 1995). A role for B cells in RA has been shown by the clinical improvement in patients depleted of B cells with regimens including the anti-CD20 mAb rituximab (Edwards *et al.*, 2002). Roles for $CD4^+$ and B cells have been more definitively shown in many mouse models.

Blockade of three different cytokines—TNF-α, IL-1, and IL-6—has been shown to be effective in ameliorating established RA (Bresnihan *et al.*, 1998; Maini *et al.*, 1999; Nishimoto *et al.*, 2002; Weinblatt *et al.*, 1999). These findings are in line with most mouse models, except that data on IL-6 are limited (see Table I). It is important to note, however, that these mediators are pleiotropic and likely operate in a wide variety of otherwise dissimilar inflammatory diseases.

Auto-Abs, most notably RF and anticyclic-citrullinated-peptide Ab, are found in RA but are of uncertain pathological significance (Morgan *et al.*, 1987; Souto-Carneiro *et al.*, 2001; Verheijden *et al.*, 1997). RA has not been transferred to naïve (in more ways than one) humans using serum (Harris and Vaughan, 1958), and rarely have human auto-Abs been shown to cause arthritis in mice (Wooley *et al.*, 1984). However, the same is true for murine PGIA, in which the indirect evidence for the importance of auto-Abs is strong.

There is little direct evidence for involvement of complement in RA. Patients deficient in C3 get severe infections, and there are no data on the incidence of RA in such patients (reviewed in Schur, 1986). Patients deficient in C1q, C2, or C4 frequently suffer from systemic lupus, and patients lacking C5 are highly susceptible to infection with *Neisseria* bacteria (reviewed in Schur, 1986); again, there are no data on the incidence of RA. A C5-blocking mAb has shown some clinical benefit in established RA in an early trial (Jain *et al.*, 1999). Additional, although indirect, evidence for involvement of complement in RA comes from the findings, apparently unique among inflammatory arthritides, that total hemolytic complement (CH50) is depleted in the synovial fluid of active rheumatoid joints (Pekin and Zvaifler, 1964; Ruddy *et al.*, 1969), and that levels of complement breakdown products are concomitantly elevated (Mollnes *et al.*, 1986; Olmez *et al.*, 1991). Deposits of Ig and C3 are found in the articular cartilage of affected joints (Cooke *et al.*, 1975; Vetto *et al.*, 1990), as in auto-Ab-mediated mouse models. The roles of FcRs have

not yet been directly evaluated in RA, but polymorphisms in the genes for FcgRIIIA and FcgRIIA may be linked to susceptibility or severity (Brun *et al.*, 2002; Morgan *et al.*, 2000; Nieto *et al.*, 2000). Mixed results have been obtained with the administration of high doses of intravenous Ig (Maksymowych *et al.*, 1996; Muscat *et al.*, 1995; Tumiati *et al.*, 1992), which may modulate FcR function, but likely has other effects (reviewed in Kazatchkine and Kaveri, 2001).

Thus, apart from the inevitably murkier results that come from working with heterogeneous human populations rather than homogeneous inbred mouse strains, RA most resembles the "active" models shown in Table I and on the left side of Fig. 2. We propose that RA—like the CIA, K/BxN, AIA, and PGIA models—is initiated by the breakdown of T cell tolerance to auto-Ag that reside in (but may not be specific to) the joint, leading to production of auto-Ab, formation of ICs, activation of cells of the innate immune system, and cytokine-mediated pathologic remodeling of joint tissues. The process may be initiated, and proceeds to a certain point, systemically rather than locally. As in the mouse models, roles for Ab-independent pathways are not excluded.

Any theory for the pathogenesis of RA must provide an explanation for RF. We will discuss two hypotheses, both of which are consistent with RA as an IC-initiated or IC-mediated disease, but that put RF in very different roles. First, RF could be an epiphenomenon, the common, nearly inevitable, consequence of chronic IC disease. B cells bearing surface IgM with RF activity are able to take up Ab-rich ICs with great efficiency and present peptides from the associated Ag to CD4^{+} T cells (Roosnek and Lanzavecchia, 1991). Thus these RF B cells could in turn receive cognate T cell help for the production of RF. It is not unreasonable to propose, as Roosnek and Lanzavecchia (1991) have, that such a mechanism normally plays a useful role in facilitating the clearance of ICs and the appropriate down-regulation of Ab responses that have served their purpose. Second, RF could serve as an amplifier of Ab-mediated disease by enhancing the activation of complement or the activation of cells through FcgRIII. Indeed, in the presence of IgG, RF can activate complement *in vitro* (Tanimoto *et al.*, 1975; Zvaifler and Schur, 1968). Thus one can envision a "two-hit" mechanism for the initiation of RA: first, an auto-Ab response to a joint-associated Ab; second, an RF response that magnifies Ab-associated effector mechanisms. Such a two-hit mechanism could explain many of the troublesome findings related to RF in both RA and mouse models. People with RF, whether with other inflammatory diseases or in good health, could remain free of RA because they do not have the primary arthritogenic auto-Ab. The 20% of RA patients who lack RF may be those whose auto-Ab response is sufficient to cause arthritis, as in the CIA and K/BxN models. It is perhaps not a coincidence that in the models in which disease can be transferred using serum (CIA, K/BxN), RF is not found, but in

models that cannot be transferred with serum, it often is (PGIA, HTLV-1, lpr). An important prediction of this hypothesis is that the addition of RF to Ab-mediated models of RA should make disease worse. To date, there is only one such report, showing a greater severity of disease with the addition of monoclonal human RF (IgM or IgG) to mice immunized with type II collagen (Ezaki *et al.*, 1996). Similar findings would need to be made in passive models of arthritis, however, to support the notion of RF as an amplifier of the effector phase. Another prediction is that rituximab and other B cell-depleting therapies should be equally effective in RF-positive and RF-negative patients, as long as production of the relevant primary auto-Ab declines. With renewed interest in auto-Ab in RA, this prediction will likely be testable in the near future.

The development of mAb-based immunological therapies, in addition to providing great benefit to patients, is allowing more precise testing of hypotheses about the pathogenesis of human RA. As was the case in the development of TNF-blocking agents, it will probably be by a fruitful combination of research on mouse models and on human patients that the reemerging paradigm of RA as an Ab-mediated disease will be assessed.

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