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Advances in Rheumatoid Arthritis Animal Models

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Abstract

Experimental models of rheumatoid arthritis (RA) have contributed immensely to our understanding of the pathogenesis as well as the treatment of this debilitating autoimmune disease. Significant progress has been made in the past few years in defining the role of newer cytokines and regulatory T cells, of inflammation-mediated bone and cartilage damage, and of the cholinergic anti-inflammatory pathway in modulating the disease process in arthritis. Furthermore, new therapeutic targets, including specific tyrosine kinases and proteasome subunits have been explored. These advances offer renewed optimism for continued improvements in the management of RA.

INTRODUCTION

Experimental models of autoimmune arthritis are an invaluable resource for studying the pathogenesis of RA as well as for the testing of new products for their anti-arthritic activity. Rodent models have increasingly been used in such studies because of the availability of genetically homogeneous inbred mouse/rat strains (Tables 1 and 2). In addition, a variety of genetically modified knockout and transgenic mice are available to dissect complex pathological events. The production of the first knockout rat using homologous recombination technology was first described in 2010. This would be an asset to investigators using rat models of arthritis. Also reported that year was a novel non-human primate model of collagen-induced arthritis (CIA) in the common marmoset. This marks a significant step towards translational research in the field of arthritis. The current review will be devoted to rodent models of experimental arthritis. Broadly, these animal models can be divided into two main subgroups- experimentally-induced (Table 1) and spontaneous (Table 2) arthritis. Despite the diversity of these models, each of them shares several features with RA.

Localization of inflammation to joints

The mechanism for preferential targeting of the joint is clear for some models but not for others. In CIA, an immune response is being directed against a joint antigen (collagen type II; CII) and in antigen-induced arthritis (AIA), the immune response is being directed toward joints by the site of antigen inoculation. In other models of arthritis however, the underlying mechanisms are not yet clear. It is mechanistically more or less evident why

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models such as the human tumor necrosis factor-α transgenic (hTNFtg), interleukin 1 receptor-α (IL-1Ra) knockout, IL-6R activating mutation knockin, or SKG mouse (with perturbed thymic selection) have an activated immune response but it is unclear why the joint bears the primary inflammatory response. In the keratinocyte specific Jun deletion model of psoriasis, loss of Jun leads to increased chemokine expression in the epidermis (1). Although this may explain the skin-directed inflammation, it is unclear why inflammation is also present in joints. Similarly, it is not known why immune responses to non-joint-specific antigens cause joint inflammation in models such as adjuvant arthritis (AA) and streptococcal cell wall-induced arthritis (SCWIA).

In the K/BxN model, autoimmunity to a ubiquitously expressed antigen, glucose-6-phosphate isomerase (GPI), causes joint specific inflammation. Difference in vascular permeability is a possible mechanism by which immune responses might be found in joints. Following intravenous K/BxN serum transfer, there is a rapid (maximum rate of leak within 3 minutes) increase in vascular leakage (2). Interestingly this vascular leak phenomenon was seen in the paw and ear but not in the cecum or back skin. Furthermore, mice deficient in mast cells, neutrophils, and Fc-gamma receptor III (FcγRIII) have no vascular leak and are also resistant to K/BxN serum-induced arthritis.

In the IL-6R knockin mouse, arthritis can be rapidly induced with adoptive transfer of T helper 17 (Th17) cells followed by induction of ‘microbleeding’ by puncture of the knee joint capsule with a needle (3). Transfer or microbleeding alone did not induce arthritis indicating that the localized extravasation of Th17 cells in a genetically susceptible mouse can initiate joint inflammation. IL-6 expression in the joint was markedly increased with transfer and microbleeding compared to either alone. The localized induction of IL-17 production has been shown to be important in other models of arthritis as well.

The cytokine responses during the course of arthritis

The cytokine-mediated events during the course of arthritis have traditionally been viewed in the context of the CD4+ Th1/Th2 paradigm, which has been the cornerstone of cytokine biology for over two decades. Over the past decade, newer cytokines of the IL-17/IL-23 axis and others (e.g., IL-27, IL-33, IL-35) have emerged that have forced renewed investigations into the immunopathogenesis of arthritis.

The CD4+ Th17 cells that secrete IL-17 represent a distinct lineage from CD4+ Th1 cells. Transforming growth factor-β (TGF-β) and IL-6 are involved in the induction of Th17, whereas IL-21 and IL-23 are required for the expansion and maintenance of these cells. IL-17 also can be produced by γδ-T cells and granulocytes, and it is chemotactic for neutrophils. Both interferon-γ (IFN-γ) and IL-4 can inhibit the activity of Th17. IL-27 is secreted by cells of the myeloid lineage and it has been shown to induce IFN-γ but to inhibit Th17 response. Furthermore, cytokines such as IFN-γ and TNF-α, that have traditionally been believed to be prototypic pro-inflammatory in nature, have now been shown to possess anti-inflammatory activity as well.

Recent studies in arthritis models have addressed two important questions regarding cytokine action: 1) what are the relative roles of IFN-γ and IL-17 in the pathogenesis of arthritis?; and 2) is IL-27 pathogenic or protective in arthritis? In regard to IFN-γ, a new aspect of its role in arthritis has emerged from observations on IFN-γ−/− mice in the CIA model (4). These mice develop more severe arthritis than their wild type counterparts. Further examination of the underlying mechanisms revealed enhanced IL-17 response in the absence of IFN-γ, highlighting the regulatory role of IFN-γ in autoimmune arthritis. These observations were supported by those in the AA model that treatment of rats with a peptide of Hsp65, that induces a predominantly Th1 response, led to the downmodulation of arthritis

(5). This was accompanied by a reduction of the IL-17 response. In another study, injection of IFN-γ in rats, after the onset of AA, resulted in reduced severity of AA (6). In the proteoglycan-induced arthritis (PGIA) model, IFN-γ−/− mice developed arthritis that was attributable to IL-17 (7). PGIA in wild type mice is predominantly a Th1-mediated disease because IL-17−/− mice developed arthritis that was similar to wild type mice. However, in the absence of IFN-γ, IL-17 performed its pathogenic role.

In the case of IL-17, mice given anti-IL-17 antibodies showed a significantly reduced incidence and severity of CIA, emphasizing the pathogenic importance of IL-17 (8). This is supported by observations in the AA model wherein treatment of rats with IL-17R-IgG1 Fc fusion protein afforded protection from AA (9), whereas injection of rats with IL-17 aggravated AA (6). In another study, the blockade of IL-17 activity by an anti-IL-17 aptamer was shown to abrogate the development of the disease in GPI-induced arthritis model (10).

IL-27 has been shown to contribute to the disease process in the PGIA model (11), but to be protective against arthritis in the CIA model (12). In the PGIA model, the pathogenic effect of IL-27 was associated with its ability to enhance the differentiation of Th1 cells producing IFN-γ (11). Furthermore, the frequency of IL-17-expressing T cells was unaffected in IL-27−/− mice. On the contrary, in the CIA model, IL-27 injection at the onset of arthritis resulted in suppression of the disease (12). This was associated with reduced levels of IFN-γ, IL-6, IL-17, and anti-CII antibodies. In the AA model, IL-27 was reported to be pathogenic in one study (13), but protective in another (6). Additional studies would be needed to sort out the reasons for the observed differences in disparate model systems as well as between studies in the same model system.

The roles of IL-7, IL-18, and IL-33 in arthritis have been clarified further with inhibitors of these cytokines (14, 15). The importance of IL-7 in the arthritogenic process has been revealed by showing that the blockade of IL-7 receptor caused a reduction in clinical arthritis as well as joint damage (16). A systemic injection of the adenovirus encoding the soluble form of the IL-18 receptor accessory protein (sIL-18Rbeta), which caused increased expression of the transgene in vivo, led to aggravation of CIA (14). This was associated with increased IL-17, but reduced IL-10 and regulatory T cells (Treg). In another study, IL-33 expression was found in the joints of mice with CIA, and the in vivo neutralization of IL-33, using antibody to the IL-1 family receptor ST2, ameliorated arthritis (15).

Control of arthritis via Treg and tolerogenic dendritic cells (DC)

The activity of the pathogenic effector T cells can be countered by a variety of regulatory T cells, including forkhead box P3 (Foxp3)-expressing CD4+CD25+ Treg. Treg develop in the thymus (natural Treg), but they also can be induced from naïve T cells in the periphery (‘Induced Treg’ or ‘Adaptive Treg’). Treg mediate their suppressive effect on the target cells either via cell-to-cell contact or via their secreted cytokines, TGF-β and IL-10. There is also a described CD8+CD25+Foxp3+ subset of Treg.

Studies in the CIA model and the K/BXN model have revealed new aspects of Treg activity. In the CIA model, treatment with IL-35 induced regression of arthritis via expansion of Treg (17). Similarly, expansion of CD4+ Treg and the induction of CD8+ Treg followed anti-CD3 treatment, resulting in arthritis attenuation (18). CD8+ Treg were efficient in inhibiting IL-17 production. In studies employing low dose irradiation, attenuation of CIA correlated with expansion of Treg and inhibition of the pro-inflammatory cytokines IL-6 and IL-17 (19, 20). In the K/BXN model, a genetic deficiency of Treg led to aggravated arthritis (21).

Besides regulatory T cells, DCs preactivated in a specific manner can render the target cells tolerant. This is a newly developing area because DCs have traditionally been viewed as immune-stimulating cells. It has been shown that adoptive transfer into mice with CIA, of CII-pulsed DCs activated by lipopolysaccharide (LPS), caused reduction in the severity of arthritis (22). This was associated with Th1/Th2 immune deviation (reduced IFN-γ but increased IL-10) but without any effect on antibodies or Treg. In another study, LPS-activated DCs had anti-arthritic activity, which correlated with expansion of Treg but without any immune deviation (23). Furthermore, these DC expressed the enzyme indoleamine 2,3-dioxygenase (IDO). This enzyme catalyzes the degradation of tryptophan, which in turn leads to cellular depletion of this essential amino acid and causes hyporesponsiveness of the target cells.

Inflammation and bone damage in arthritis

There is growing realization about the relationship between inflammation and bone damage. Immune system activation and bone damage share some of the critical mediators such as pro-inflammatory cytokines (TNF-α, IL-1β, IL-6 and IL-17), the receptor activator of nuclear factor-kB ligand (RANKL) and RANK. Although these shared pathways allow activated immune cells to induce osteoclast differentiation and bone resorption, there is also evidence that osteoclast differentiation and bone resorption can be targeted independently of overall joint inflammation. This underscores the need to better understand the relationship between inflammation and bone damage. The T cell subsets (e.g., Th2 and Treg) and the cytokines (e.g., IL-4, IL-10) that are involved in regulation of pathogenic effector Th1/Th17 responses also serve as inhibitors/regulators of osteoclastogenesis and bone damage. Osteoblasts also secrete osteoprotegerin (OPG), which acts as a decoy receptor for RANKL and induces protection against bone damage. In this regard, RANKL/OPG ratio serves as one of the indicators of bone damage.

It has recently been shown that IL-17 can upregulate RANK on osteoclast precursors, which leads to enhanced RANKL signaling and bone loss (24). Furthermore, IL-17 is not required for normal osteoclastic activity, which emphasizes the role of IL-17 in inducing bone damage during inflammatory arthritis (24). Another T cell-derived cytokine that may contribute to inflammation-associated bone damage is SOFAT (Secreted Osteoclastogenic Factor of Activated T cells), which can induce osteoclast formation in RANKL-independent manner (25). On the contrary, overexpression of the promoter (GATA3) for Th2 cells can protect against inflammation and bone erosion as shown in the methylated bovine serum albumin (mBSA)-induced arthritis model (26).

A study in the CIA model has brought to light the role of natural killer (NK) cells in bone damage (27). NK cells derived from the joints of these mice express RANKL, and the depletion of NK cells ameliorated inflammation as well as bone erosions. An opposite manipulation with Treg consisting of increasing the number/activity of Treg led to protection against bone damage in hTNFtg mice (28). This could be achieved by injecting the hTNFtg mice with bone marrow from Foxp3-transgenic mice or with CD28 superagonist antibody. Studies based on inhibiting/blocking RANKL in the CIA and AA models revealed the dissociation between inflammation and bone damage such that bone loss was prevented without much effect on inflammation (29). However, there was no effect on the formation of bony spurs along the joints, suggesting that this process was independent of RANKL (29).

The disruption of critical cellular signaling pathways in osteoclasts and/or mature osteoblasts can afford protection against bone damage in arthritis. This has been shown by inhibiting mammalian target of rapamycin signaling (mTOR) in hTNFtg mice using sirolimus or everolimus (30), and by transgenic disruption of glucocorticoid signaling in K/

BXN mice by the overexpression of 11β-hydroxysteroid dehydrogenase under the promoter for type I collagen (31).

A new dimension has been added to the area of bone homeostasis by the observation that sphingosine-1-phosphate (S1P), a lipid mediator that has previously been shown to regulate leukocyte trafficking from the lymphoid tissues, induce chemotaxis, and regulate the migration of osteoclast precursors in vivo (32). The osteoclast precursors express S1P1 receptors and exhibit positive chemotaxis along an S1P gradient. The effect of S1P on the motility of osteoclast precursors was further elucidated using two agonists of S1P1, SEW2871 and FTY720. These results point to potentially new therapeutic targets aimed at modulating S1P-mediated events in osteoclastogenesis.

Inflammation and cartilage damage in arthritis

Just as it is possible to reduce bone damage independently of overall joint inflammation, it is possible to dissociate cartilage damage from overall joint inflammation. Cadherin-11, a transmembrane cell-adhesion molecule expressed on synovial lining cells, can be detected in normal synovium but its expression increases in inflamed synovium (33). Mice lacking functional cadherin-11 have a markedly attenuated synovial lining layer. When arthritis was induced using the K/BxN serum transfer model, cadherin-11 knockout mice had a roughly 50% reduction in inflammation as assessed by clinical score and ankle swelling. Similar reductions in the severity of arthritis could be reproduced in wild-type mice by disrupting normal cell-cell interactions using anti-cadherin-11 antibody or a cadherin-11-Fc fusion protein. Histologically, inflammatory pannus can attach to bone and adjacent cartilage, causing full thickness erosion of the underlying cartilage. Pannus attachment and bone erosion were unaffected in the cadherin-11 deficient mice but interestingly, the pannus did not extend onto the adjacent cartilage and cartilage erosion was markedly decreased.

Chemokines and adhesion molecules in arthritis

Chemoattractant cytokines (chemokines) and their receptors direct the migration of arthritogenic leukocytes from the peripheral circulation into the joints. A variety of adhesion molecules also play an active role in the process of cell migration. IL-17 has been shown to induce the migration of monocytes into sponges grafted in severe combined immunodeficient (SCID) mice, and this migration, in part, involved the induction of CC chemokine ligand 2 (CCL2)/monocyte chemoattractant protein-1 (MCP-1) (34). Similarly, IL-18 injected into the graft efficiently recruited monocytes to the injection site as tested in the RA synovial tissue-SCID mouse chimera (35). In another study using the same experimental model of arthritis, serum amyloid protein A (A-SAA) induced the migration of circulating monocytes into the graft (36).

The blocking of specific chemokine receptors revealed a protective, rather than pathogenic effect, on the development of arthritis (37, 38). Blockade of eotaxin-2 using specific antibodies significantly reduced the severity of AA (37). In contrast, mice genetically deficient in CC chemokine receptor 5 (CCR5) as well as mice treated with Met-RANES (methionylated-Regulated upon Activation, Normal T-cell Expressed, and Secreted), a CCR5 inhibitor, developed aggravated arthritis compared to the controls (38). Also, the integrin avβ3 has been exploited as a target for selective delivery of anti-angiogenic drug fumagillin into the arthritic joints using nanoparticles, and this treatment resulted in suppression of inflammatory arthritis (39).

Leukocyte-endothelial interaction is an attractive target for the treatment of arthritis and other inflammatory diseases. In this regard, the identification of developmental endothelial locus-1 (Del-1) as an endogenous leukocyte-endothelial inhibitor secreted by endothelial

cells in vivo is of special interest (40). Del-1 deficiency in endothelial cells enhanced LFA-1-dependent leukocyte adhesion, and mice deficient in Del-1 showed higher neutrophil accumulation in the inflamed site (40). Thus Del-1 could be exploited as a therapeutic target for arthritis. Further study of Del-1 may also provide clues into the initiation of arthritis in experimental models. A study in the CIA model has highlighted the genetic control of leukocyte-endothelial interaction (41). Multiple quantitative trait loci (QTL) controlling this cell-cell interaction were identified, as were several expression QTL that influenced the expression of certain adhesion molecules and cytokines involved in this process.

Cholinergic anti-inflammatory pathway and its influence on arthritis

Smoking has been invoked as one of the environmental factors in a subset of RA patients. Nicotine is one of the components of cigarette smoke and is a stimulator of α7-nicotinic acetylcholine receptors (α7nAChRs). Increasing evidence is accumulating that points to the role of the vagus nerve and α7nAChRs in modulating inflammation and autoimmune responses.

Studies in the CIA model have revealed that modulation of the cholinergic anti-inflammatory pathway can significantly alter the frequency and/or severity of arthritis. In one study, mice were subjected either to vagotomy or treated with nicotine. The former aggravated arthritis, whereas the latter suppressed the disease (42). These results were supported by another study from the same group showing that CIA was aggravated in α7nAChR-knockout mice. However, another group reported the opposite results in mice lacking this receptor (43).

At present, the precise reasons for nicotine-induced protection versus aggravation of arthritis are not fully defined. In this context, a recent study in the AA model has highlighted a novel attribute of nicotine's effects on arthritis (44). The timing of nicotine administration, in regard to disease induction, had a significant effect on arthritis. Nicotine pretreatment aggravated arthritis, whereas nicotine posttreatment afforded protection against the disease (44). These effects correlated well with alterations in the pro-inflammatory cytokines and anti-cyclic citrullinated peptide (aCCP) antibodies. This study also was the first to report the presence of aCCP during the natural course of AA. At present, the target antigens affected by citrullination in the joints of arthritic rats are not defined. Results showing that an arthritogenic aCCP monoclonal antibody interacted primarily with the citrulline residue (45), should advance our understanding of the citrullination process in the pathogenesis of arthritis in different animal models as well as RA patients.

New therapeutic targets for arthritis under investigation

Over the past decade, biologics aimed at blocking or neutralizing the action of the pro-inflammatory cytokines (e.g., TNF-α, IL-1, IL-6) have extensively been tested, and some of these are now in clinical use in the treatment of RA. However, not all RA patients respond well to these agents. Trials with p38α failed to hold the promise projected from studies in animal models. Nevertheless, significant efforts are underway to identify and explore new therapeutic targets for arthritis.

Among these are the protein tyrosine kinases upstream of p38 [spleen tyrosine kinase (Syk) and Janus kinase (JAK)] and the proteasome. Syk plays a critical role in several biological processes including the adaptive immune response, osteoclast maturation and vascular development. In addition, Syk regulates the mitogen-activated protein kinase (MAPK) signaling in synovial fibroblasts. A small molecule Syk inhibitor was shown to suppress arthritis in the CIA model (46). Syk inhibitor not only suppressed inflammatory clinical arthritis, but also synovitis, pannus formation and bone erosions. Furthermore, a study using

the K/BXN serum transfer model has revealed the significant role played by Syk in the pathogenesis of arthritis (47). Mice that were genetically deficient in Syk in the hematopoietic compartment were significantly protected from clinical inflammatory arthritis as well as bone and cartilage damage compared to the controls (47). The Syk inhibitor pro-drug, Fostamatinib, is now in Phase III clinical trials.

JAKs are cytoplasmic tyrosine kinases that integrate signaling from several cytokines and growth factors. The cytokines that bind to their cognate receptors coupled with a common gamma chain signal through JAK1 and JAK3. CP-690550, an inhibitor of JAK3 that also has activity against JAK1 and JAK2, is in six Phase III Clinical trials in RA patients. WYE-151650, a JAK3-selective inhibitor has been shown to be effective in suppressing clinical and histopathological arthritis in the CIA model (48). The new test compound compared favorably with CP-690550 tested in the same study. Thus, inhibition of JAK3 alone was sufficient to inhibit CIA.

Proteasome inhibitors represent another category of potential therapeutic products for arthritis. The proteasome plays an important role in the degradation of cellular proteins. The production of many of the pro-inflammatory cytokines and other immune mediators is controlled by a master transcription factor NF-kB. The activity of NF-kB itself is controlled by the degradation of its regulator, IkB. In addition, the proteasome may have other effects on immune pathways involved in arthritis. Treatment of rats with a proteasomal inhibitor MG132 significantly reduced arthritis-associated pain and inflammation in the AA model (49). Another proteasome inhibitor that had selectively for one of the subunits of the proteasome, low molecular mass polypeptide 7 (LMP7), afforded protection against arthritis in the CIA model as well as the collagen antibody-induced arthritis (CAIA) model (50). Presumably, a proteasome subunit-specific compound might have much less toxicity than that causing a generalized inhibition of multiple active subunits of the proteasome.

Conclusion

The diversity of experimental models of arthritis has been an asset in elucidating the mechanisms underlying the disease process in autoimmune arthritis. As none of these models has all the features of RA, and the immune effector pathways involved vary from model to model, the information obtained by studying these models is complementary. In the past few years, notable advances have been made in our understanding of the disease process (e.g., the role of more recently described cytokines such as IL-17, IL-23, and IL-27; and of Treg) as well as in developing and testing novel therapeutic agents (e.g., inhibitors of Syk and JAK-3). Intensive efforts have been made to define further the relationship between inflammation and bone/cartilage damage and between cholinergic anti-inflammatory pathways and arthritis severity. It is anticipated that the increasing application of genomics and proteomics to research problems in autoimmune arthritis will be rewarding in the very near future. Similarly, novel manipulations of siRNA, microRNA and stem cells may also advance our understanding of many aspects of autoimmune arthritis.

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Keywords

RA Rheumatoid arthritis

CIA	Animal models; Collagen-induced arthritis
AA	Adjuvant arthritis
GPI	Glucose-6-phosphate isomerase
PGIA	Proteoglycan-induced arthritis
IL	Cytokines; Interleukinγ
TNF-α	Tumor necrosis factor-a
IFN-γ	Interferon-g
Treg	CD4+CD25+ regulatory T cells
DC	Dendritic cells
RANKL	Inflammation; Receptor activator of nuclear factor-kB ligand
OPG	Osteoprotegerin
Del-1	Chemokines; Developmental endothelial locus-1
aCCP	Anti-cyclic citrullinated peptide
α7nAchRs	antibody; α7-nicotinic acetylcholine receptors
S1P	Sphingosine-1-phosphate
Syk	Spleen tyrosine kinase
JAK	Janus kinase

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Table 1

Models of experimentally-induced arthritis in rodents

Model	Rat/mouse	Examples of arthritogens	Disease transferable to recipients via
Adjuvant-induced.arthritis (AA)	Rat	Heat-killed.*M. tuberculosis* H37Ra or *M. smegmatis*	T cells
Antigen-induced.arthritis (AIA)	Mouse/Rat	Methylated bovine.serum albumin (BSA)	T cells
Avridine-induced arthritis (AvIA)	Rat	Avridine (CP20961)	T cells
Collagen-induced arthritis (CIA)	Mouse/Rat	Type II collagen (CII)	Antibodies & T cells
GPI induced arthritis	Mouse	Glucose-6-phosphate isomerase	Unknown, but likely antibodies
Immune complex-mediated arthritis (ICA)	Mouse	Antigen and the corresponding antibody	-
Pristane-induced arthritis (PIA)	Mouse/rat	Pristane	T cells
Proteoglycan-induced arthritis (PGIA)	Mouse	Cartilage proteoglycan (aggrecan)	T cells
Streptococcal cell wall-induced arthritis (SCWIA)	Rat	Group A/B/C streptococci	T cells

Table 2

Models of spontaneously developing arthritis in rodents

Mouse model	Arthritogenic effector mechanism	Disease transferable to recipients via
IL-1Ra knockout mice	Genetic deficiency of IL-1 receptor antagonist(IL-1Ra)	T cells
IL-6R knockin	Tyrosine to phenylalanine point mutation in GP130 subunit of IL6 receptor causes enhanced IL-6 signaling	T cells
Inducible Jun knockout	Deletion of JunB and c-Jun proteins in keratinocytes using cre-lox system leads to increae in chemokines production	Unknown
K/BxN	Crossreactive autoantibodies against glucose-6-phosphate isomerase (GPI)	Antibodies
SKG	A defective thymic selection of T cells due to a mutation in the SH2 domain of ZAP 70	T cells
TNF-α-transgenic	Increased TNF-α production	TNF-α
TS1xHACII mice	Transgenic mice having CD4+ T cells bearing T cell receptor specific for influenza hemagglutinin (HA), and co-expressing HA under the class II promoter	Unknown