Review
The role and clinical implications of G6PI in experimental models of rheumatoid arthritis

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Abstract

The antigens that trigger the pathogenic immune response in rheumatoid arthritis (RA) remain unknown. Until recently it was assumed that either viral or microbial antigens, or joint-specific antigens were the target of arthritogenic T and B lymphocytes in RA. Consequently, murine models of arthritis are induced by immunization with either joint-specific antigens such as type II collagen or microbial products such as streptococcal cell wall. In the K/B×N T-cell receptor transgenic mouse model arthritis is caused by a systemic autoimmune response to the ubiquitously expressed glycolytic enzyme glucose-6-phosphate isomerase (G6PI). The autoreactive transgenic T cells recognize G6PI and provide help for the production of arthritogenic IgG antibodies against G6PI. More recently it was shown that G6PI immunization induces severe symmetrical peripheral polyarthritis in genetically unaltered DBA/I mice. In that model CD4+ T cells are necessary not only for the induction but also for the effector phase of arthritis. Here we review the pathomechanisms that lead from systemic autoreactivity to arthritis in these models, consider the relevance of anti-G6PI immune reactivity for RA, and discuss the insights into the pathogenesis of RA and possibly other autoimmune conditions that can be gained from these models.

Keywords: arthritis, CD4+ T lymphocytes, DBA/I mice, FCγ receptors, glucose-6-phosphate-isomerase

Introduction

The aetiology of rheumatoid arthritis (RA), which affects approximately 1% of the population, remains obscure. There is considerable evidence suggesting that RA is an autoimmune disease in which autoreactive lymphocytes trigger macrophages, synoviocytes and other effector cells that mediate synovitis and the destruction of cartilage and bone [1–7].

B and T lymphocytes in rheumatoid arthritis and experimental models

Approximately two-thirds of RA patients produce rheumatoid factors – autoantibodies that are directed against IgG [8]. Because of this strong and diagnostically relevant association, B lymphocytes were long suspected to be the main culprits in RA pathogenesis [1,8]. RA susceptibility and severity are strongly associated with certain HLA-DR haplotypes in Caucasians [9]. The discovery of this linkage led to a more T-cell centred view [3,9–13] because antigen presentation to T lymphocytes is the only known immunological function of MHC class II molecules such as HLA-DR. The difficulty in detecting cellular immune responses against autoantigens in RA patients [14–16], together with the failure of some T-cell directed immunomodulatory treatment strategies [17–22] and impressive successes of therapeutic tumour necrosis factor (TNF)-α blockade in RA, appeared to implicate macrophages as the major effector cells in the clinically overt stages of RA [7,23].

Most recently, however, two different lines of evidence re-assert the importance of T cells. First, a large clinical trial

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CIA = collagen-induced arthritis; CII = collagen type II; G6PI = glucose-6-phosphate isomerase; IL = interleukin; MHC = major histocompatibility complex; RA = rheumatoid arthritis; TCR = T-cell receptor; Th = T helper; TNF = tumour necrosis factor.

[24] showed clear clinical benefits from treating active RA by blocking T-cell costimulation and activation. Second, a spontaneous point mutation in the gene encoding an Src homology 2 (SH2) domain of ZAP-70, a key signal transduction molecule in T cells, causes chronic auto-immune arthritis in mice that resembles human RA in many respects [25]. Moreover, the pathogenic importance of B lymphocytes is again becoming appreciated [26,27], partly because depletion of these cells has been shown to be a successful treatment for RA patients [28]. Taken together, a consensus is beginning to emerge that many different cell types, both from the innate and the adaptive immune systems, are crucial to the pathogenesis of RA [4].

Arthritogenic cartilage antigens?

Although some autoantibodies, such as rheumatoid factors that recognize IgG and antibodies against citrullinated antigens, have diagnostic significance [8,29,30], the autoantigen(s) that are recognized in chronic inflammatory arthritides such as RA are unknown [5,16,22,31,32]. Collagen type II (CII) is the major protein in articular cartilage. It is a candidate autoantigen for RA because antibodies and perhaps T cells against CII occur in patients with RA [5,33–35] and because it is arthritogenic in animals [36]. Collagen-induced arthritis (CIA) has thus become the most intensively studied murine model for human inflammatory arthritides [37].

Autoantibodies are important players in CIA. Adoptive transfer of either polyclonal IgG antibodies purified from the sera of arthritic mice [38–40] or combinations of monoclonal antibodies against CII [41] can induce arthritis even in mouse strains that are not susceptible to actively induced CIA [38]. This form of adoptively transferred arthritis has been called CII antibody-induced arthritis [42]. Antibodies against CII are also found in the blood and joints of some RA patients [33,34,43,44]. In contrast, the role of T lymphocytes in the pathogenesis of CIA is less clear. Collagen-specific proinflammatory T cells can be demonstrated in the blood and synovial fluid of mice with CIA [45]. However, most attempts to induce CIA in mice by T-cell transfer have been unsuccessful [46] and CD4-deficient mice develop CIA with unaltered incidence and severity [47]. Mice lacking α/β T cells are resistant to CIA, whereas γ/δ T cells are neither necessary nor protective. A single report on CIA, albeit at reduced severity as compared with wild-type littermates, in *rag*-deficient DBA/1 mice [48] has not been corroborated by others to date. Taken together, the question regarding how T cells operate in the pathogenesis of CIA has not yet been answered definitively.

CII-specific T cells have also been difficult to demonstrate in the blood or synovial fluid of RA patients [15,49–51]. Moreover, attempts to treat RA by inducing T-cell tolerance to CII have yielded disappointing results [18,19,22,52]. Taken together, there is little solid evidence that CII or any other single joint-specific antigen such as collagen type XI [53], gp39 [54], cartilage oligomeric matrix protein [55], or cartilage proteoglycan (aggrecan) [56] is a diagnostically or pathogenetically significant autoantigen in all RA patients. Given the complexity and clinical and pathological diversity of RA, it seems more likely that different autoantigens are important in different subsets of RA patients.

Arthritogenic noncartilagenous antigens?

Some noncartilagenous antigens have been used to induce and study arthritis in mice and rats [37]. These are either various microbial compounds with adjuvant effects and/or antigenic properties as in adjuvant arthritis, CpG induced arthritis, or streptococcal cell wall induced arthritis [57–61]; or antigens directly injected into the joints of experimental animals following systemic immunization (antigen-induced arthritis) [62,63]. These arthritides are not the subject of this review because the inciting noncartilagenous antigens are non-self antigens. The importance of noncartilagenous self-antigens to the pathophysiology of arthritis had not been considered until recently.

Autoreactivity against a systemically expressed antigen causes symmetrical peripheral polyarthritis in TCR transgenic K/B×N mice

A T-cell receptor (TCR)-transgenic mouse model of arthritis has challenged the concept that arthritis necessarily results from an autoimmune attack against joint-specific antigens. When C57BL/6 mice expressing a transgene-encoded TCR recognizing amino acids 41–61 of bovine ribonuclease bound to the MHC molecule I-A^k (the 'KRN' receptor) were inadvertently crossed with diabetes-susceptible NOD mice, all of the F1 offspring (the K/B×N mice) spontaneously developed peripheral symmetrical polyarthritis [64]. Arthritis in the K/B×N mice resembles RA in that it symmetrically affects the small peripheral joints. In contrast to RA, the distal interphalangeal joints are regularly affected in K/B×N mice, there are no systemic manifestations, the mice do not produce rheumatoid factors, and the arthritis does not remit [64]. Thus, K/B×N mice spontaneously develop peripheral polyarthritis that resembles human RA in many clinical and pathological respects. This surprising finding induced intense research into the pathophysiology of arthritis in the K/B×N mice.

KRN T cells and I-Aβ^{g7} molecules are necessary for the induction but not the effector phase of arthritis in K/B×N mice

Both the KRN TCR and one copy of the NOD I-Aβ^{g7} MHC molecule are necessary for development of arthritis in K/B×N mice. Neither KRN TCR transgenic C57BL/6 mice nor the F1 from crosses of the transgene-expressing C57BL/6 mice with strains other than the I-Aβ^{g7}-bearing

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NOD mice develop arthritis. KRN T cells proliferate in response to I-Aβ^{g7}APC in the absence of experimentally added antigens [65]. Importantly, Th cells are only necessary in the induction phase of arthritis. Once the pathogenesis has passed a certain point, Th cells are dispensable. Treatment with anti-CD4 antibodies is ineffective if it is started less than 5 days before the onset of arthritis. What, then, are the effector mechanisms that induce arthritis in K/B×N mice? Using adoptive transfer experiments and a variety of knockout mice, Mathis and colleagues [65] demonstrated that immunoglobulin is responsible for arthritis induction in K/B×N mice. Transfer of serum (as little as 100 μl) or IgG antibodies from arthritic K/B×N mice induced arthritis in recipient mice of different strains, even in *rag-2*$^{-/-}$ mice that lack T and B lymphocytes [65]. What do these autoantibodies recognize?

The pathogenic autoantibodies recognize a ubiquitously expressed glycolytic enzyme

Quite surprisingly, the target antigen recognized by both the transgenic T cells and the pathogenic autoantibodies was not joint-specific but the ubiquitously expressed glycolytic enzyme glucose-6-phosphate isomerase (G6PI, or GPI) [66]. G6PI, also known as phosphohexose isomerase, catalyzes the interconversion of fructose-6-phosphate and glucose-6-phosphate [67]. It is an essential glycolytic enzyme, expressed by all cells, and G6PI deficiency is lethal at the two-cell stage [68].

Arthritis can be induced in recipient mice by transfer of polyclonal IgG$_1$ or combinations of at least two different monoclonal IgG$_1$ antibodies against G6PI [69]. Mice that lack the activating FcγRIII are less susceptible to arthritis induced by transfer of K/B×N serum than are normal mice, pointing to FcγRIII$^+$ effector cells in arthritis pathogenesis [70,71]. K/B×N serum transfer arthritis in mice that lack the inhibitory FcγRII has been reported to be similar [70,71] or more severe than in wild-type littermates [72].

Complement, neutrophils and mast cells are all indispensable for arthritis development

In the K/B×N transfer arthritis IgG$_1$ antibodies against G6PI induce several different effector functions of the innate immune system; the alternative pathway of the complement cascade is triggered, resulting in chemotactic activity (but not the membrane attack complex) [70,71]. Neutrophils [73] and mast cells [74] are both required as effector cells to mediate joint destruction.

IL-1 is important but neither TNF-α or IL-6 is needed for arthritis development in K/B×N mice

In contrast to RA in humans and most other murine models of arthritis, neither TNF-α or IL-6 is needed for arthritis development in K/B×N mice [75,76]. TNF-α is an important mediator of joint destruction in RA and several murine models of it [7]. Therefore, the K/B×N model yielded another surprising finding when it turned out that TNF-α blockade had no effect on the development and progression of arthritis [75]. Moreover, K/B×N serum induced arthritis in mice that were deficient for both TNF receptor-1 and TNF receptor-2, or lymphotoxin-α with the same incidence and severity as in normal littermates [76]. In that same study a somewhat reduced incidence of arthritis was noted upon serum transfer in TNF-α-deficient mice obtained from one particular colony as compared with wild-type controls. However, that difference was not found with TNF-α-deficient mice obtained from a different colony [76]. Similarly, and again in contrast to previous findings in other murine models of arthritis [77], IL-6 deficiency had no influence on the development of K/B×N serum transfer arthritis [76].

Taken together, the above findings indicate that recognition of a ubiquitously expressed self-antigen by T cells that bear a transgenically encoded receptor and escape negative selection in the thymus [78] induces an arthritogenic autoantibody response, which then triggers innate immune effector mechanisms to induce arthritis.

Autoreactivity against G6PI in the pathogenesis of RA?

This perplexing and informative model raises the question of whether autoreactivity against G6PI is relevant to the pathogenesis of human RA or other chronic inflammatory arthritides. One initial report [79] indicated that IgG antibodies against G6PI were detectable at low dilution (1:50) in the serum of 64% of RA patients but not in control individuals.

However, a number of other investigators did not find increased levels of α-G6PI antibodies in the serum of patients with RA [80–83], collagen tissue disease [81–83], or other chronic arthritides [81,83,84]. Moreover, the commercial G6PI preparation used in the initial study was found to be contaminated with other proteins, and RA sera contained antibodies against some of these other proteins [81]. Taken together, these findings indicate that antibodies against G6PI are not diagnostic markers for RA. An interesting further twist in the story was added by a recent report. van Gaalen and coworkers [85] found that whereas only one of 55 RA patients who did not have systemic manifestations of the disease produced antibodies against G6PI, seven of 22 patients with systemic manifestations (nodules or vasculitis) and 12 of 13 patients with Felty's syndrome had detectable α-G6PI antibodies in their sera [85]. Thus, the possibility remains that antibodies against G6PI occur frequently in Felty's syndrome. However, it is currently not yet clear whether the increased seropositivity is specific for antibodies against G6PI or a sign of generally dysregulated auto-antibody production in patients with Felty's syndrome, and

the data must be independently confirmed. Another group [86] compared α-G6PI antibody titres in serum and synovial fluid and found increased concentrations of α-G6PI antibodies in the synovial fluid of RA patients. Taken together, the currently available data argue against a pathogenic role for anti-G6PI immune responses in RA.

Are the immunological events that induce arthritis in the K/B×N model relevant to RA?

Even if G6PI is not a relevant autoantigen to RA pathogenesis, the question remains of whether the immunological events that lead to the development of arthritis in the K/B×N model are involved in human RA. Both experimental and clinical data strongly support the possibility that autoreactivity against systemically expressed autoantigens may result in organ-specific autoimmune disease.
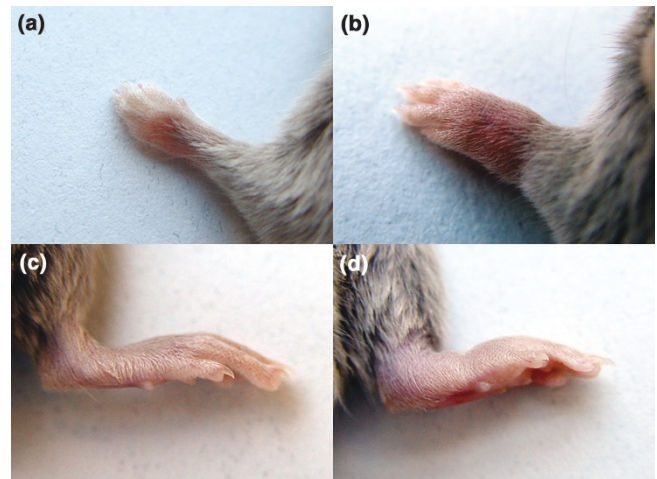
Systemic autoreactivity causes peripheral neuritis in TCR transgenic mice

The K/B×N model is not the only transgenic model in which organ-specific autoimmunity develops as a consequence of systemic self-reactivity of T cells. Oono and coworkers [87] produced transgenic mice that express Eα$_{52-68}$ covalently bound to the I-A^b molecule as their only MHC peptide complex. These mice spontaneously develop a CD4$^+$ Th cell dependent peripheral nervous system-specific autoimmune disease. Neuritis in these TCR transgenic mice shares many of the histopathological features found in experimental autoimmune neuritis, including demyelination and axon degeneration [87]. Serum from these transgenic mice did not stain peripheral nerves and could not transfer the disease to other animals [87].

Autoantibodies against systemically expressed autoantigens are diagnostically important in organ-specific autoimmune diseases

There are several clinical examples of autoantibodies against systemically expressed autoantigens that are highly sensitive and specific diagnostic markers for certain organ-specific autoimmune diseases. These include the anti-Jo-1 autoantibodies that bind to and inhibit activity of histidyl-tRNA synthetase, and the autoantibodies that recognize proteasomes that are found in different but overlapping subsets of myositis patients [88–90]; the antimitochondrial antibodies (AMA-2) that recognize the E2 subunit of mitochondrial pyruvate dehydrogenise [91], which are found in patients with primary biliary cirrhosis; the autoantibodies against proteinase 3 (c-ANCAs) in Wegener's granulomatosis [92]; and, of course, the rheumatoid factors that recognize IgG antibodies [8]. All of these autoantibodies are directed against systemically expressed autoantigens, yet they are highly specific and sensitive markers for the respective diseases. However, their pathogenic significance remains unknown, partly because of the lack of suitable animal models.
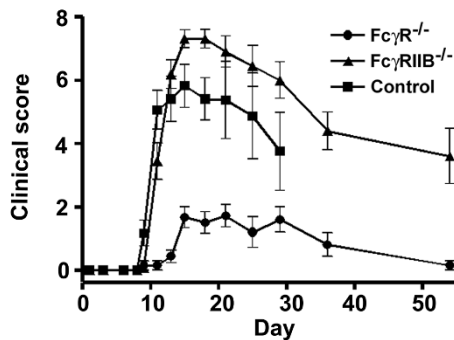
Figure 1

(a, b) Front and **(c, d)** hind limbs from DBA/1 mice that had been immunized with glucose-6-phosphate isomerase (G6PI) subcutaneously (panels b and d) or administered phosphate-buffered saline subcutaneously (panels a and c) 14 days earlier. From [93], © 2004. The American Association of Immunologists, Inc. Reprinted with permission.

Systemic autoreactivity causes severe peripheral symmetrical polyarthritis in genetically unaltered mice

To bridge the gap between the potentially very informative yet rather artificial transgenic mouse models and the situation in patients, we considered whether a systemic immune response against G6PI could induce joint-specific pathology in genetically unaltered mice. Of several inbred strains tested, DBA/1 mice, the same inbred strain of mice that is also susceptible to CIA, develop severe symmetrical peripheral polyarthritis arthritis following one single immunization with recombinant human or murine G6PI in adjuvant [93] (Fig. 1). The incidence of arthritis upon immunization is in excess of 90%, and the time course is uniform and highly predictable. Clinical signs of arthritis are first visible 9 days after immunization; the arthritis then rapidly progresses, reaches its maximum at about day 14 after immunization, and then slowly resolves. The pattern of joints affected is similar to but not identical to that observed in RA; wrists, metacarpal joints, proximal and distal interphalangeal joints are affected at the front limbs, and the tarsal, ankle and knee joints at the rear limbs. Neither the spine, nor the hip, elbow, or shoulder were affected in any of the animals analyzed [93]. Histologically, there are no further signs of inflammation past day 21. Instead, reorganization and fibrosis become visible. Importantly, there were no pathological findings in any other organs apart from the joints. The sudden onset, and high incidence and severity of arthritis distinguishes this model from CIA. The spontaneous remission of G6PI-induced arthritis in genetically unaltered DBA/1 mice is

Figure 2

Arthritis scores of (■) DBA/1 wild-type, (●) DBA/1 FcγR common γ-chain deficient, and (▲) DBA/1 FcγRIIB deficient mice. Data are presented as mean clinical scores ± standard error of the mean only for those mice that developed arthritis. Arthritis incidence was 10/11 in DBA/1 wild-type, 8/24 in DBA/1 FcγR common γ-chain deficient, and 16/16 in DBA/1 FcγRIIB deficient mice. From [93], © 2004. The American Association of Immunologists, Inc. Reprinted with permission.

one important clinical difference from the transgenic K/B×N model. This allows for the study of the immunological mechanisms that modulate the autoimmune response and induce remission of the disease.

Continuous requirement for Th cells in the pathogenesis of G6PI-induced arthritis

Th cells are needed throughout the effector cells in G6PI-induced arthritis in normal mice. Depletion of CD4+ cells immediately after immunization prevents arthritis. More importantly, depletion of CD4+ cell on days 11 and 14 (i.e. when clinical symptoms are at their maximum) induces rapid remission of arthritis both clinically and histologically [93]. Thus, in G6PI-induced arthritis in normal mice, CD4+ cells are not only important in the induction but also throughout the effector phase of the disease. This is in contrast to the K/B×N model, in which Th cells are only necessary to provide help to B cells that produce the arthritogenic antibodies against G6PI. Once these antibodies are produced, T cells are no longer necessary for arthritis development in the K/B×N model, and transfer of serum or antibodies from arthritic K/B×N mice [66,69] can transfer arthritis to naïve recipients of almost any mouse strain. Similarly, CIA can be transferred by antibodies or serum [38–41] and it can be induced even in the absence of CD4+ cells [47,48].

IgG antibodies are necessary but not sufficient for G6PI-induced arthritis in normal mice

DBA/1 mice that lack the FcγR common γ chain and thus cannot signal through the activating FcγRI and FcγRIII are protected from G6PI-induced arthritis. In addition, mice that lack the inhibitory FcγRIIB develop severe and prolonged G6PI-induced arthritis (Fig. 2) [93]. Therefore, IgG antibodies and FcγR+ effector cells are necessary for the development of G6PI-induced arthritis. Nevertheless, arthritis cannot be induced in naïve recipients by transfer of serum or antibodies from arthritic DBA/1 mice [93]. It is currently unclear why G6PI-induced arthritis cannot be transferred with serum from arthritic animals; it is possible that the antibodies present in the serum some 14 days after immunization lack the necessary affinity for G6PI. Thus, unlike the CIA and K/B×N models, both CD4+ T cells and antibodies are necessary for the development of G6PI-induced arthritis, and neither transfer of T cells nor transfer of antibodies alone can induce arthritis in recipient mice. TNF-α is indispensable for the development of G6PI-induced arthritis in normal mice; treatment of mice with the soluble p75 TNF receptor (etanercept) completely prevents the development of arthritis [93].

Taken together, the above findings indicate that G6PI-induced arthritis in genetically unaltered mice provides a reliable and robust model in which the induction, effector phase and modulation of organ-specific disease induced by systemic autoimmunity can be dissected and therapeutically targeted. Thus, G6PI-induced arthritis narrows the gap between the TCR transgenic K/B×N model and the situation in patients. Some of the major clinical and immunological similarities and differences between CIA, the K/B×N model and G6PI-induced arthritis are summarized in Table 1. Several important questions remain unanswered.

Why the joint?

It is currently unclear why systemic autoreactivity against the ubiquitously expressed glycolytic enzyme G6PI specifically induces arthritis, with no other symptoms of organ-specific or systemic autoimmune disease. Interestingly, although GPI is ubiquitously expressed in the body, the immune response against GPI appears to initiate in the draining lymph nodes of peripheral joints in K/B×N mice [94]. The reasons for this early localized immune response are currently unclear but these findings suggest that something unique to the joints initiates a local immune response to a systemic autoantigen. This contention is further supported by positron emission tomography studies [95,96] that demonstrate rapid localization of adoptively transferred antibodies against G6PI to the peripheral joints of the recipient mice.

It is known that cationic antigens such as G6PI bind well to cartilage [62,97]. However, systemically expressed antigens such as G6PI are not only presented in the joint, and not every cationic antigen induces arthritis upon immunization. Immune complexes are a critical component in the pathogenesis of K/B×N serum transfer arthritis [96,98] and for G6PI-induced arthritis in normal mice (unpublished observations). G6PI deposits, together with IgG and C3, are detectable in the joints of arthritic mice in

Table 1

Clinical and pathological characteristics of different arthritis models in mice

Characteristics	Arthritis model		
	Collagen-induced arthritis	K/BxN arthritis	G6PI-induced arthritis
Arthritogenic antigen	Cartilage specific (CII)	Systemic (G6PI)	Systemic (G6PI)
Susceptible strain	DBA/1	KRN TCR transgenic × NOD F1 mice	DBA/1
Arthritis induction	CII immunization and boost	Spontaneous	G6PI immunization
Pathogenic cells and effector mechanisms			
T cells	?	Induction phase	Induction and effector phases
Antibodies	Necessary and sufficient	Necessary and sufficient	Necessary
FcγRI or FcγRIII necessary	+	+	+
FcγR II	+	+ or − in different studies	+
C5	+	+	+
Mast cells	Uncertain	+	Unknown
Neutrophils	+	+	Unknown
Macrophages	Uncertain	Unknown	Unknown
TNF-α	+	(±)	+
IL-1	+	+	Unknown
IL-6	+	+	Unknown
Spontaneous remission	+	−	+

CII, type II collagen; G6PI, glucose-6-phosphate isomerase; TNF, tumor necrosis factor.

the K/B×N serum transfer model [98]. G6PI–IgG immune complexes are also visible in the glomeruli of arthritic K/B×N mice. In contrast to the joints, however, the immune complexes in the kidney were not colocalized with C3 [98]. It is has therefore been suggested that G6PI–immunoglobulin immune complex trigger the complement cascade exclusively in the joints. This would be explained by the absence of membrane-bound C3 inhibitors from chondrocytes [98]. The question remains as to why only a particular pattern of joints is arthritic in the K/B×N model and in G6PI-induced arthritis. Furthermore, immune complex diseases do not necessarily induce erosive arthritis. Systemic lupus erythematosus provides a classical example; there, the immune complex induces glomerulonephritis but not erosive arthritis.

Why G6PI?

Currently, there is no mechanistic explanation for the association between autoantibodies against certain systemically expressed antigens and particular auto-immune diseases [8,88–92]. Similarly, it is not clear why G6PI becomes the target of an arthritogenic autoimmune response in K/B×N and DBA/1 mice. In addition to its function as a glycolytic enzyme, G6PI can be secreted and serves a variety of other physiological functions [99]. G6PI is identical to neuroleukin, a neurotrophic factor for spinal and sensory neurones [100,101], which is associated with terminal sprouting; autocrine motility factor [102], which stimulates motility via a receptor-mediated pathway [103]; and maturation factor, which mediates the differentiation of human myeloid leukemic HL-60 calls to terminal monocytic cells [104].

A receptor for G6PI, namely gp78, has been identified. Gp78 is a transmembrane protein, a RING finger-dependent ubiquitin protein ligase (E3) of the endo-plasmatic reticulum [105,106]. It remains to be investigated whether one or more of these physiological functions of G6PI contribute to its immunogenicity and arthritogenicity.

Conclusion

The search for arthritogenic autoantigens has long focused on joint-specific antigens. The TCR transgenic K/B×N model of arthritis and more recently G6PI-induced arthritis in genetically unaltered mice have demonstrated that a noncartilagenous systemically expressed self-antigen can be the target of an arthritogenic immune response. Although the two models exhibit clinical and pathophysiological differences, a complex interplay between cells and effector mechanisms of both the adaptive and innate immune system is necessary in each model. Whereas autoreactivity against G6PI does not

seem to play a role in RA, there are well known clinical examples of autoantibodies that are directed against autoantigens that are systemically expressed but pathognomonic for organ-specific diseases, and the possibility that arthritis may be induced by systemic autoreactivity remains interesting and plausible. G6PI-induced arthritis provides a model in which both the induction and modulation of arthritis induced by autoreactivity against noncartilagenous antigens can be studied.

Competing interests
The author(s) declare that they have no competing interests.

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