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Role of Toll like receptor-activated dendritic cells in the development of autoimmunity

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1. ABSTRACT

The recognition of microbial stimuli by Toll-like receptors (TLRs) expressed on dendritic cells (DCs) is essential for the regulation of immune responses. DC activation via TLRs leads to the production of proinflammatory cytokines, chemokines and surface molecules that play a key role in the regulation and control of inflammatory reactions and adaptive immunity. Minor imbalances in the feedback control of TLR-activated innate immune cells have been associated with autoimmunity in genetically prone individuals. We review here recent studies indicating how TLR-mediated activation of innate immune cells, including DCs, may be involved in the development and/or maintenance of autoimmune responses in the presence of both endogenous and exogenous ligands.

2. INTRODUCTION

Genetic susceptibility and environmental factors are the key elements in the development of autoimmune diseases. Many studies have provided insights into the molecular events leading to autoimmune responses. Microbial infections, particularly those caused by viruses, have long been thought to induce autoimmune diseases in genetically prone individuals (1, 2). Viral infections induce four different processes that may account for the activation of autoimmune reactions and the possible precipitation of autoimmune diseases (3). The first process is that virus-mediated tissue destruction may generate new tissue-specific antigens for non-tolerant, naive T cells (3). Alternatively, the autoimmune response may be induced by the differential processing of self-peptides. Indeed, after

viral infections, interferons (IFNs) are secreted by both activated virus-specific Th1 cells and virus-infected cells. IFNs up-regulate the immune functions of antigen-presenting cells (APCs), which then start to engulf self-peptides. The activation of APCs by cytokines can induce an increase in protease production and a change in the processing of captured self-epitopes, resulting in the production of "cryptic" epitopes. The presentation of "cryptic" epitopes can lead to the activation of self-reactive Th1 cells and self-tissue destruction (4). In a third mechanism, the immune responses generated against viruses induce the release of cytokines that could activate autoreactive T cells in a bystander reaction (5). According to a final mechanism, viral antigens can trigger autoimmune reactions by molecular mimicry of endogenous peptides (6). Herpes stromal keratitis (HSK) provides a classical example of viral molecular mimicry. HSK is an autoimmune disease of the eye induced by herpes virus infections. It has been shown that this disease is mediated by $CD4^+$ T cells that cross-recognise a corneal epitope and an epitope of the UL6 viral protein in genetically susceptible mice (7). Following viral infection, autoreactive T cells recognising the UL6 protein are activated and destroy the corneal tissue (8). These four mechanisms are not mutually exclusive and may intersect.

Recently, it has been proposed a different mechanism by which microbes might induce autoimmune responses - through innate rather than adaptive immunity. Microbial invasions are sensed by the pattern recognition receptor (PRR)-expressing cells of the innate immune system. PRRs bind microbial products collectively referred to as micro-organism-associated molecular patterns (MAMPs) (9). Toll-like receptors (TLRs) are the best characterised PRRs (10). The recognition of MAMPs by TLRs expressed on DCs (11) plays an essential role in the regulation of immune responses. This interaction leads to a complex genetic reprogramming of DCs, involving the sequential acquisition of different regulatory functions in innate and adaptive immunity (12). However, an increasing number of reports have shown that, in a susceptible genetic background, DC activation via TLRs can induce autoimmune tissue destruction, particularly through the production of type I IFNs.

3. DCs, TLRs AND AUTOIMMUNITY

3.1 DCs, TLRs and type I IFNs

DCs are crucial regulators of both innate and adaptive immune responses (13, 14). After encountering a pathogen, DCs efficiently process antigens for their presentation in association with MHC molecules. However, before DCs can prime the adaptive immune response, they must complete a full maturation process initiated by direct exposure to microbial ligands (15). Interaction with pathogens results in DC activation. Activated DCs migrate to the T-cell area of the lymph nodes, where the antigen-specific cells of the adaptive immune response can be primed. Early studies on DCs indicated they originated in the bone marrow, with developing precursors migrating from the bone marrow to the blood. DCs have been found in the heart, liver, thyroid, pancreas, bladder, kidney, ureter, gut, lungs and skin. Fully developed DCs have also been observed in the circulatory networks of the body, including blood and afferent lymphatic vessels. DCs display a high degree of plasticity within organs and lymphoid tissues. Various DC phenotypes have been described, based on tissue distribution and the surface expression of particular markers (16-18). Immature DCs in mice are characterised by the expression of CD11c, low levels of the costimulatory molecules CD80 and CD86, and low levels of MHC class II; all these molecules may be up-regulated at the cell surface upon activation (19). Interestingly, DCs can also express the T-cell markers, CD4 and CD8. In the lymph node, some DCs have been found to be $CD4^-CD8^-CD11b^+$ and to express moderate levels of the scavenger receptor CD205 (20). An additional DC phenotype has been found in skin-draining lymph nodes: these DC cells produce large amounts of langerin, a molecule typically produced by Langerhans cells (LC), a population of immature DC located in the skin (19). Finally a DC population with a different function — IFN-producing plasmacytoid DCs (pDCs) — has been described in mouse blood and lymph nodes (21).

Human DC phenotypes have been less well characterised. Human DCs do not express CD8 and DCs expressing CD11b, CD11c and CD4 have been described in the spleen and tonsils (18). IFN-producing pDCs express $CD45RA^+CD123^+$ and are $CD11c^-$ (22).

Resident DCs and DCs recruited from the blood can sense the presence of a pathogen in an inflamed tissue through TLRs and other PRRs. The signal transmitted by these receptors is crucial for DC maturation and migration to secondary lymphoid tissues.

Thirteen different TLRs have been identified in mammals (23). Some of these receptors — TLRS 1-6 and 11 — are expressed at the cell surface and recognise different products of bacterial, fungal or protozoan origin, including lipopetides, lipopolysaccharides and peptidoglycans. Others, such as TLRs 3, 7, 8 and 9, are located in the endoplasmic reticulum and recognise microbial nucleic acids (23). TLRs can also bind an ample set of endogenous ligands, such as heat shock proteins (HSP), hyaluronate and heparan sulphate (extracellular matrix breakdown products), fibronectin, high mobility group box 1 protein (HMGB1) and modified low-density lipoproteins (24). By recruiting different combinations of adapter proteins, individual TLRs turn on signal transduction pathways leading to the activation of different transcription factors, such as nuclear factor (NF)-κB, activation protein (AP)-1, and interferon regulatory factors (IRFs) (25).

The DC maturation process leads to DCs releasing various cytokines and chemokines (26) — including type I IFNs, key cytokines directing innate immune responses and favouring the subsequent development of adaptive responses to viruses and bacteria — within a few hours of microbial infection. Type I IFNs are encoded by 13 IFN-alpha and one IFN-beta gene, clustered on chromosome 9 and having an unusual, intron-less structure. The products

of all these genes signal via the IFN-alpha/betaR pathway. Type I IFNs are produced by many cells in response to viral challenge. However, DCs, and pDCs in particular, produce large amounts of these cytokines (27, 28), which may also have an autocrine effect on DCs, promoting their activation (29).

TLRs 7 and 9 can induce type I IFN production and are expressed at high levels in both human and mouse pDCs, as can TLRs 3, 4 and 9 in myeloid DCs (25). TLR stimulation may lead to the activation of two different signalling cascades leading to IFN production: the MyD88/IRAK-1 pathway downstream from TLR7, TLR8 and TLR9, and the Trif/IKKε pathway downstream from TLR3 and TLR4 (30-33). Activation of the Trif/IKKe pathway leads to the phosphorylation, dimerisation, and nuclear translocation of IRF-3, which is critical for IFN-beta induction, and the activation of NF-κB and AP-1, which is also required to trigger the production of inflammatory cytokines. The pathways downstream from TLR7-9 are MyD88/IRF-7-dependent (25).

In addition to playing a central role in immunity, TLR-induced type I IFNs have recently been shown to be players in the development of autoimmune responses, particularly in systemic lupus erythematosus (SLE) (34, 35).

3.2. SLE

SLE is a chronic systemic autoimmune disease characterised by the presence of autoantibodies that react with self-components in the nucleus and cytoplasm — mostly macromolecular complexes of proteins and nucleic acids. Autoantibodies generate immune complexes that accumulate in various tissues, including the kidney in particular, and cause inflammation. This disease predominantly affects women and patients present with various symptoms. Cutaneous lesions are the most common symptom, but patients may also present nephritis, pericarditis, pleuritis, painful joints, fatigue and neuropsychiatric abnormalities. Some patients die, due to renal failure and atherosclerosis.

3.2.1 Role of type I IFNs in SLE

Several lines of evidence suggest that type I IFNs may be involved in the pathogenesis of this disease. SLE patients have high levels of IFN-alpha in serum and affected tissues (36). Moreover, the repeated administration of IFN-alpha in patients suffering from various malignancies or chronic viral infections and the development of symptoms associated with SLE have been shown to be directly related (37, 38). Global gene expression studies on blood lymphoid cells and kidneys from SLE patients have shown selective up-regulation of IFN-regulated genes (IFN signature) (36, 39). Some typical lupus symptoms have been described in individuals with trisomy affecting the type I IFN gene cluster (40) and single nucleotide polymorphisms in the *IRF5* and tyrosine kinase 2 (*TYK2*) genes, both of which are involved in regulating type I IFN production (41, 42). Type I IFN has been shown to play a role in lupus in genetically susceptible NZB mice, in which deletion of the common subunit of the type I IFN receptor reduced the severity of disease and repeated injections of IFN-alpha accelerated the development of lupus symptoms (43). These findings indicate that type I IFNs are major mediators of lupus pathogenesis in mice.

3.2.2 Role of TLRs in SLE

Immune complexes isolated from the sera of SLE patients can efficiently induce the production of IFN-alpha by pDCs (44), and a mixture of IgG purified from lupus patients and apoptotic or necrotic cells constitutes a stimulus for pDC activation that is sensitive to DNase and RNase (44). Immune complexes form individuals with SLE cannot stimulate pDCs previously treated with anti-FcγRIIa antibody. As stated above, pDCs constitutively express TLR7 and TLR9 (45). These receptors were originally identified as binding viral single stranded RNAs and hypomethylated CpG motifs in bacterial DNAs, respectively. Based on these observations, *in vitro* experiments have been carried out and have suggested that the internalisation of nucleic acid-containing immune complexes by pDCs, via FcγRs, may deliver nucleic acid MAMPs to intracellular TLR7 or TLR9, triggering signalling from these receptors, leading to cell activation and type I IFN production (reviewed in (46)).

Common SLE autoantigens may become available to the immune system, leading to the formation of immune complexes, following excessive tissue damage or inefficient clearing of apoptotic cells during inflammatory processes (47). In physiological conditions, macrophages, which do not express TLR9 and TLR7 in humans, rapidly clear the debris. However, if this clearance is delayed or there are autoantibodies specific for the antigen released during tissue damage, the resulting complexes may be taken up by pDCs (46, 48). Autoreactive antibodies may be present due to defects in B cell-mediated tolerance, such as defects in receptor editing in the bone marrow and spleen, and other genetic factors in susceptible individuals (49, 50). There may therefore be a number of reasons for the massive production of autoreactive antibodies in lupus-prone subjects. Autoreactive B cells may be directly activated through TLRs and self-reactive BCR during infections (51, 52). Alternatively, autoreactive B cells may be activated by molecular mimicry, a typical example of this being provided by the cross-reactivity between the peptide derived from Epstein-Barr virus nuclear antigen 1 (EBNA1) and peptides derived from the autoantigens Ro and Sm (proteins associated with RNA-containing macromolecules) (53). TLR-mediated tolerance breakdown may also occur. Following bacterial or viral infections, DCs begin to produce type I IFNs and pro-inflammatory cytokines, leading to the priming of autoreactive T helper cells and the subsequent activation, expansion and further differentiation of autoreactive B cells (34).

The involvement of TLRs in the pathogenesis of SLE has been investigated *in vivo* in various mouse models of lupus. Mice carrying the *lpr* mutation lack the functional form of CD95 (FAS) and develop a lymphoproliferative disease associated with the production of antibodies against double-stranded DNA, chromatin and small nuclear

ribonucleoprotein particles (snRNPs). Backcrossing these mice with mice deficient for the TLR adaptor protein MyD88 results in a decrease in autoantibody levels (54, 55). Clear-cut results have also been obtained with lupus-prone TLR7-deficient mice. *Lpr/lpr* TLR7-deficient mice have low titers of autoreactive lupus-associated antibodies and develop less severe disease, with fewer activated pDCs (56). Moreover C57BL/6 mice with a knock-in for the heavy and light chains of an anti-ssDNA and RNA pathogenic antibody lose B cell-mediated tolerance in a TLR7-dependent manner (57). Finally, the causal genetic lesion in the y-linked autoimmune accelerating (*yaa*) locus, which causes a potent autoimmune disease in BXSB lupus-prone mice, involves translocation of the *Tlr7* gene from the X chromosome onto the *yaa* Y chromosome (58). This duplication results in the overexpression of TLR7 and an increase in the strength of *in vitro* responses to this TLR in *yaa*-bearing males (58). A direct cause-effect relationship was recently established between duplication of the *Tlr7* locus and disease development. Considerable increases in TLR7 expression lead to autoantibody production, DC proliferation and excessive inflammatory cytokine secretion, and these phenomena are sufficient to induce autoimmunity (59).

Published results on the involvement of TLR9 obtained *in vivo* are more controversial (reviewed in (60). TLR9-deficient *lpr/lpr* mice produce large numbers of dsDNA-specific antibodies and display more severe disease (61). Similarly, mice transgenic for a constitutive active form of phospholipase Cγ2 (PLCγ2) — another model of lupus — produce large numbers of nucleus-specific antibodies and aggravation of the disease in the absence of TLR9 (62). This protective effect of TLR9 may be due to TLR9 playing a role in the production of autoantibodies for clearing subcellular structures capable of binding several TLRs (reviewed in (60)). Nevertheless, TLR9 deficiency has been shown to have a positive effect on the disease in at least one mouse model of SLE: lupus-prone C57BL/6 mice lacking the inhibitory FcγRIIb receptor. In the absence of TLR9, autoreactive B cells do not undergo class switching to the pathogenic isotypes IgG2a and IgG2b, resulting in the presence of smaller numbers of immune complex deposits in the glomeruli and improving survival (63).

Overall, the data obtained in these studies suggest that TLRs play a fundamental role in the production of pathogenic autoantibodies and, possibly, in disease development, by inducing type I IFN production.

3.2.3. Models of disease development

Based on the above clinical and experimental observations, two different models of disease development have been proposed (46, 60). In both cases, DC-derived type I IFNs are the central factor, but in the first model, viral infections are considered to trigger disease development, whereas, in the second, disease initiation is mediated by endogenous TLR ligands (apoptotic material) in the absence of infection (Figure 1).

According to the first model, viral infections induce IFN-alpha production by pDCs, promoting cell death, the release of RNA-based autoantigens, TLR7 up-regulation by B cells and the activation of pDCs, which subsequently respond more strongly to immune complexes. Autoreactive B cells may take up RNA autoantigens through the BCR and deliver them to TLR7. This process induces B-cell activation, proliferation and differentiation. Differentiated B cells produce autoantibodies, which form immune complexes that are taken up by pDCs via FcγRs and delivered to TLR7. This increases IFN-alpha production by the pDCs, via a self-perpetuating feedback loop and causes disease maintenance (46) (Figure 1).

In the second model, also known as the two-phase model, initiation of the disease is mediated by apoptotic cell material, which is taken up by a specialised subclass of lymphoid DCs through TLRs. These DCs produce large amounts of type I IFNs, inducing the maturation of lymphoid and myeloid DCs. Mature myeloid DCs are potent APCs and activate autoreactive T helper cells, which are otherwise quiescent. Primed T helper cells contribute to the activation of autoreactive B cells. Alternatively, mature DCs may directly activate autoreactive B cells that have interacted with the antigen via the BCR, through the production of B lymphocyte stimulator protein (BlyS) and proliferation-inducing ligand (APRIL) (64). Activated, autoreactive B cells proliferate and differentiate into autoantigen-producing plasma cells. Immune complexes are thus formed that induce further type I IFN production by pDCs (which take up the immune complexes via FcγRs) and enhance B-cell proliferation and autoantibody production (60) (Figure 1).

3.3. Role of TLRs in other autoimmune diseases

Innate immune cell activation through TLRs leads to the production of proinflammatory cytokines, chemokines and surface molecules playing a key role in the regulation and control of inflammatory reactions and adaptive immunity. As for the two models of SLE development described above, a delicate imbalance in the feedback control of TLR-activated innate immune cells — DCs in particular — may lead to autoimmunity in genetically prone individuals. Many experimental results obtained in mice and multiple clinical observations suggest that TLR activation is a general phenomenon required for the development and/or chronic maintenance of various autoimmune diseases, although no clear evidence has yet been provided for a link between TLR mutations and autoimmunity. Indeed, conflicting reports have been published concerning the possible association between a TLR4 polymorphism and ulcerative colitis (65, 66), and studies on patients with rheumatoid arthritis (RA) found no clear association with TLR2 and TLR4 polymorphisms (67).

3.3.1. TLR involvement in autoimmune arthritis: clinical evidence and mouse models

RA is a chronic autoimmune disease characterised principally by synovial tissue inflammation. DCs and macrophages are generally thought to be the critical mediators in the pathogenesis of this complex disease (68-70). Clear evidence that TLR signalling pathways are activated in RA has recently emerged. TLR2, TLR4 and

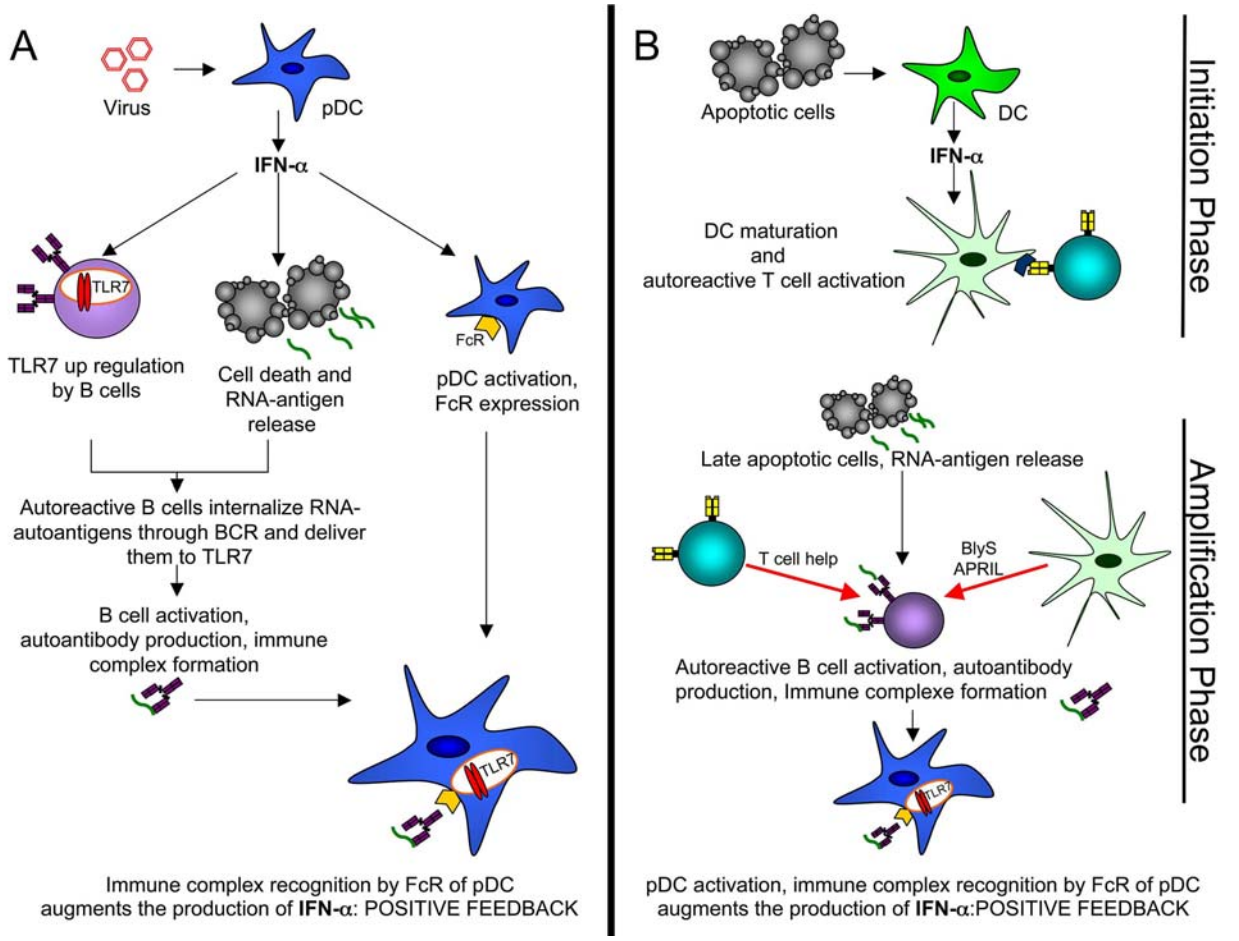

Figure 1. Models to describe the development and maintenance of SLE. (A) Viral infections elicit IFN-alpha production by pDCs. IFN-alpha induces TLR7 upregulation on B cells, tissue damage with the release of RNA-antigens and further pDC activation. Autoreactive anti-nucleic acid B cells take up RNA-antigens through the BCR and deliver them to intracellular TLR7. This induces autoreactive B-cell activation, autoantibody production and the formation of immune complexes, which are internalised by pDCs through the Fc receptor, leading to further activation and the establishment of positive feedback. (B) In the initiation phase, early apoptotic cells elicit IFN-alpha production by DCs. IFN- alpha induces DC maturation. Mature DCs can activate autoreactive T cells. In the amplification phase, late apoptotic cells release RNA-antigens. Anti-nucleic acid B-cell activation occurs through either the direct intervention of activated DCs or with assistance from T cells. Autoreactive B-cell activation leads to the secretion of autoreactive anti-nucleic acid antibodies and the formation of immune complexes. Immune complexes can activate pDCs through TLR7, establishing positive feedback.

TLR3 ligands of both microbial and endogenous origin have been detected in the joints of RA patients (71-73). These ligands can clearly induce the expression of activation markers and production of inflammatory cytokines by DCs (72). An analysis of synovial tissues in RA patients showed that TLR2 and TLR3 are expressed in synovial lining fibroblasts in addition to cells of bone-marrow origin (73, 74). The expression of TLR2 and TLR3 by synovial fibroblasts is of prime importance, as these receptors make it possible for endogenous and microbial ligands to stimulate these cells to produce inflammatory cytokines and tissue-destroying matrix metalloproteinase (73, 75).

It remains unclear from clinical observations whether TLR engagement induces RA occurs secondarily to inflammatory processes in the joints. However, classical mouse models of RA suggest that TLR pathway activation is directly involved in disease development. Indeed, intra-articular administration of streptococcal cell wall fragments, dsRNA, or CpG-containing DNA - acting mostly through TLR2, TLR3 and TLR9, respectively - can induce arthritis (76-78). Moreover, TLR4 activation with LPS has been shown to reactivate arthritis in mouse models of collagen-induced and antigen-induced arthritis (79-81). Similarly, MyD88-deficient and TLR2-deficient mice are resistant or partially resistant to streptococcal cell wall fragment-induced arthritis (76), and TLR4 inhibition with a specific antagonist reduces disease severity in the collagen-induced arthritis model and in IL-1 receptor antagonist-deficient mice — a spontaneous arthritis model (82). The TLR4 antagonist used, a highly purified LPS from

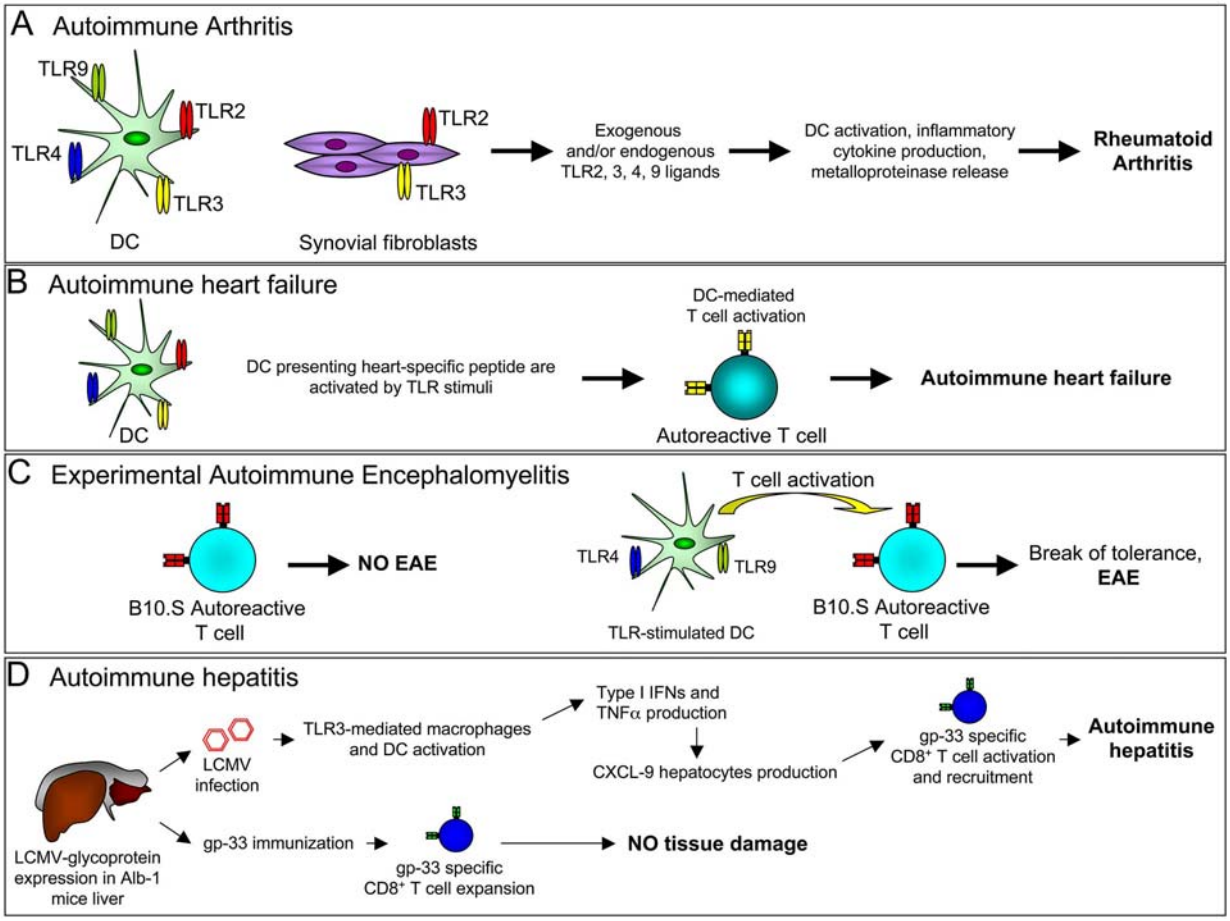

Figure 2. Role of TLRs in various autoimmune diseases. (A) In autoimmune arthritis, exogenous and endogenous ligands can activate DCs and synovial fibroblasts in joints, leading to the production of inflammatory substances, which may exacerbate the disease. (B) In mouse models of autoimmune myocarditis, TLR-activated DCs loaded with heart-derived peptides can activate autoreactive T cells, leading to autoimmune heart failure. (C) In a mouse model of experimental autoimmune encephalomyelitis (EAE), tolerance breakdown is induced by TRL4- or TLR9-activated DCs, which prime autoreactive TCR-transgenic T cells. (D) In a mouse model of autoimmune hepatitis, tolerance breakdown occurs due to LCMV infections, leading to the activation of TLR3 on macrophages or DCs. Upon activation, cells secrete type I IFNs and TNF-alpha, which induce the release of CXCL9 by hepatocytes. CXCL9 recruits autoreactive T cells to the liver, leading to tissue destruction. In the absence of TLR3 activation, immunisation with viral protein does not induce autoimmunity.

Bartonella quintana, inhibits TLR4-induced DC maturation by both endogenous and exogenous ligands (82).

3.3.2. Other autoimmune diseases: mouse models

TLR-mediated tolerance breakdown and autoimmunity have been demonstrated in other experimental models of disease (Figure 2). For instance, it is possible to induce autoimmune heart failure by injecting TLR-stimulated DCs loaded with a heart-specific self-peptide into mice (83). TLR activation and the stimulation of autoreactive $CD4^+$ T cells seem to be a prerequisite for disease in this model. As both genetic susceptibility and microbial infections are involved in the pathogenesis of dilated cardiomyopathy, the results obtained suggest that autoimmunity is not necessarily induced by antigenic mimicry, being instead triggered by tissue injury and the activation of innate immune cells via innate receptors in susceptible individuals (83) (figure2).

TLR signalling also seems to play a role in the induction of experimental autoimmune encephalomylelitis (EAE) (84). B10.S EAE-resistant mice expressing a transgenic TCR specific for the encephalitis-causing myelin proteolipid protein do not develop EAE, despite having a high frequency of self-reactive T cells. The occurrence of EAE seems to be controlled by APC activation state. The stimulation of APCs via TLR4 and TLR9 results in tolerance breakdown and the development of autoimmunity (84), consistent with the innate immune system playing an important role in maintaining the equilibrium between tolerance and autoimmunity (84) (Figure 2).

TLR activation has also been shown to be essential for the induction of autoimmunity in Alb-1 mice, a mouse model of hepatitis. These mice produce the LCMV-glycoprotein exclusively in the liver, under control of the albumin promoter (85). The LCMV-glycoprotein $peptide_{33}$-

$_{41}$ (gp-33) is processed and presented to $CD8^+$ T cells by the $H\text{-}2D^d$ molecule. The gp-33 peptide is not presented in the thymus, so gp33-specific T cells reach peripheral lymphoid organs in steady-state conditions but do not cause autoimmunity. Nevertheless, the infection of animals with LCMV induces the expansion and activation of self-reactive (anti-gp33) T cells and hepatitis. Viral infection has been shown to be essential for disease development, as the immunisation of Alb-1 mice with gp-33 peptide, despite inducing the expansion of autoreactive T cell populations, did not cause tissue damage (85). The key element of viral infection required for disease development proved to be TLR activation. LCMV infection promotes autoimmunity via TLR3 engagement on macrophages and various DC subsets, leading to the production of type I IFNs and TNF-alpha, which in turn activate other DCs and bone marrow-derived cells. Moreover, type I IFNs and TNF-alpha also induce the secretion of chemokines, such as CXCL9, from hepatocytes. These chemokine attract self-reactive T cells to the liver, where they cause tissue destruction. CXCL9 has been also implicated in other autoimmune diseases. For instance, it is present at high concentration in the synovial fluids of patients with rheumatoid arthritis (86). The Alb-1 mouse model clearly demonstrates that the TLR-mediated activation of DCs and other bone marrow-derived cells is involved in tolerance breakdown and autoimmune precipitation in susceptible individuals (Figure 2). A loss of tolerance and autoimmunity were also observed in an analogous mouse model in which the LCMV-glycoprotein was produced exclusively in the beta-cells of the pancreas, under control of the rat insulin promoter (87). Autoimmune beta-cell destruction was induced by viral infection or the administration of viral protein together with TLR3 or TLR7 agonists. As in the hepatitis model, disease development was strictly dependent on IFN-alpha production (87). Various hypotheses have been proposed concerning the way in which IFN-alpha causes destructive insulitis, including IFN-alpha-mediated overexpression of MHC class I molecules on beta-cells, resulting in an increase in beta-cell susceptibility to $CD8^+$ T-cell lysis (87), IFN-alpha increases $CD8^+$ T-cell lytic functions and the efficiency of LCMV-glycoprotein cross-presentation by DCs (88) (Figure 2).

In conclusion, *in vitro* and *in vivo* studies have provided clear evidence that, for some autoimmune diseases, TLR-mediated DC activation by endogenous or exogenous stimuli and type I IFN production may contribute to autoimmune symptoms in genetically susceptible individuals, if not regulated by fine feedback mechanisms. It remains unclear whether TLR activation on DCs is the mechanism by which the disease is induced, or rather a phenomenon required for disease maintenance.

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