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Mast cells in rheumatic disease

Jolien Suurmond [a,1,2], Daniël van der Velden [a,b,1], Johan Kuiper [b], Ilze Bot [b], René E.M. Toes [a,*]

[a] Department of Rheumatology, Leiden University Medical Center, Albinusdreef 2, PO Box 9600, 2300 RC Leiden, The Netherlands
[b] Division of Biopharmaceutics, Leiden Academic Centre for Drug Research, Einsteinweg 55 2332 RA Leiden, The Netherlands

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ABSTRACT

Rheumatoid Arthritis is a chronic autoimmune disease with a complex disease pathogenesis leading to inflammation and destruction of synovial tissue in the joint. Several molecules lead to activation of immune pathways, including autoantibodies, Toll-Like Receptor ligands and cytokines. These pathways can cooperate to create the pro-inflammatory environment that results in tissue destruction. Each of these pathways can activate mast cells, inducing the release of a variety of inflammatory mediators, and in combination can markedly enhance mast cell responses. Mast cell-derived cytokines, chemokines, and proteases have the potential to induce recruitment of other leukocytes able to evoke tissue remodeling or destruction. Likewise, mast cells can secrete a plethora of factors that can contribute to tissue remodeling and fibroblast activation. Although the functional role of mast cells in arthritis pathogenesis in mice is not yet elucidated, the increased numbers of mast cells and mast cell-specific mediators in synovial tissue of rheumatoid arthritis patients suggest that mast cell activation in rheumatoid arthritis may contribute to its pathogenesis.

1. Pathogenic pathways in rheumatoid arthritis

Rheumatoid arthritis is a systemic autoimmune disease characterized by chronic inflammation of the synovial lining of the joint, and is one of the most common autoimmune diseases affecting approximately 1% of the general population (Gabriel, 2001). Synovitis, inflammation of the synovial tissue, is mediated through leukocyte infiltration of the tissue, and leads to hyperplasia of fibroblast-like synoviocytes and tissue remodeling. Likewise, synovitis can induce cartilage destruction and bone erosion, ultimately leading to destruction of the joint. Clinically, synovitis induces pain and swelling of the involved joints, and the tissue destruction evoked can lead to disabilities if left untreated.

It is currently believed that different cells of the immune system play a role in the pathogenesis of rheumatoid arthritis. However, the exact cause of rheumatoid arthritis is not known. Genetic risk factors (such as HLA) underlying disease susceptibility are often involved in T- and B-cell responses and the presence of activated B cells and T cells in the inflamed synovium of rheumatoid arthritis patients indicate that adaptive immunity plays a prominent role. Furthermore, the presence of autoantibodies in the majority of patients points towards an important role for B cells in rheumatoid arthritis. However, besides the role of adaptive immune cells in initiation of autoreactive responses, innate immune cells are thought to play an important role during the effector phase by sustaining inflammation.

Treatment is usually aimed at lowering disease activity via immunosuppression, which can be achieved in various ways including through the interference with B cell-mediated immunity, co-stimulatory pathways, and inhibition of proinflammatory cytokines, suggesting that these pathways play an important role in disease pathogenesis.

* Corresponding author. Tel.: +31 715261290.
E-mail addresses: jsuurmond@nshs.edu (J. Suurmond), d.van_der_velden@lumc.nl (D. van der Velden), j.kuiper@lacdr.leidenuniv.nl (J. Kuiper), i.bot@lacdr.leidenuniv.nl (I. Bot), r.e.m.toes@lumc.nl (R.E.M. Toes).
[1] These authors contributed equally to this work.
[2] Present address: Center for Autoimmune and Musculoskeletal Diseases, The Feinstein Institute for Medical Research, North Shore-LIJ Manhasset, New York 11030, USA.

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1.1. Autoantibodies

A major effector function thought to contribute to pathogenesis in rheumatoid arthritis is mediated by autoantibodies. The classical autoantibody system associated with rheumatoid arthritis is rheumatoid factor, which recognizes the Fc portion of IgG. However, rheumatoid factor is not specific for rheumatoid arthritis patients, as it is also produced in a number of other inflammatory conditions, therefore its role in disease pathogenesis is often questioned. An important group of autoantibodies in rheumatoid arthritis targets modified proteins, with anti-citrullinated protein antibodies (ACPA) being the most well-characterized. These antibodies recognize a variety of proteins or peptides in which the amino acid arginine is modified into a citrulline through a posttranslational modification process mediated by Peptidyl Arginine Deiminase (PAD) enzymes. PAD enzymes are normally present inside cells and can be activated by high calcium levels when cells, such as neutrophils, undergo apoptosis, an event readily occurring during inflammation (Gyorgy et al., 2006). PAD enzymes that are transported to the outside of cells can citrullinate the extracellular matrix and in doing so can create targets for ACPA. Citrullinated proteins can be found in a variety of inflamed tissues, including the synovial tissue of rheumatoid arthritis patients (Baeten et al., 2001; Makrygiannakis et al., 2006). ACPA can recognize many citrullinated proteins such as vimentin, filaggrin, and fibrinogen. Because fibrinogen and vimentin are also present in the extracellular matrix of the synovium, these proteins are often considered as important target antigens for ACPA (Klareskog et al., 2008).

ACPA show a very high specificity for rheumatoid arthritis, and are present in the majority (~70%) of rheumatoid arthritis patients (Nishimura et al., 2007; Schellekens et al., 2000). Since their discovery ACPA are mainly used as diagnostic marker. However, it is now becoming increasingly clear that ACPA might also play a functional role in the pathology of rheumatoid arthritis. Several observations underlie this notion. ACPA can be observed already years before the onset of symptoms, and rarely develop after onset of clinical manifestation of rheumatoid arthritis (Rantapaa-Dahlqvist et al., 2003; Ronnelid et al., 2005). The latter indicates that it is not likely that ACPA are a consequence of the inflammation present in rheumatoid arthritis patients. ACPA+ and ACPA- patients differ considerably with respect to the underlying genetic and environmental risk factors, suggesting that rheumatoid arthritis consists of two different disease entities: ACPA+ and ACPA- rheumatoid arthritis (Huizinga et al., 2005; Klareskog et al., 2006; Pedersen et al., 2007; van der Helm-van Mil et al., 2006). Furthermore, ACPA+ and ACPA- rheumatoid arthritis patients have a different disease course with ACPA+ patients having a more progressive disease, characterized by increased radiological joint damage and worse disease activity scores (Meyer et al., 2003; Ronnelid et al., 2005). These findings suggest that ACPA contribute to disease pathogenesis.

When ACPA antibodies are adoptively transferred into mice with a low-level synovial inflammation caused by anti-collagen antibodies, ACPA (reactive with citrullinated fibrinogen or collagen II) could enhance arthritis, implicating their direct involvement in the inflammatory process (Kuhn et al., 2006; Uysal et al., 2009).

Other autoantibodies present in rheumatoid arthritis patients include antibodies directed against carbamylated proteins, or anti-Carbamylated Protein Antibodies (anti-CarP), another autoantibody directed towards modified proteins. Like ACPA, Anti-CarP are present before disease onset and associate with disease severity in (ACPA-negative) rheumatoid arthritis patients, and could potentially contribute to disease pathogenesis (Shi et al., 2011).

1.2. Toll like receptor ligands

Toll like receptor (TLR) activation is another important pathway for immune activation in rheumatoid arthritis. Although TLR are particularly known for their role in protection against pathogens, through their recognition of pathogen associated molecular patterns, endogenous ligands have been reported to trigger these receptors as well. Such endogenous ligands are present in conditions of stress or tissue damage, and often are intracellular molecules that can be either passively or actively released upon cell death. As rheumatoid arthritis, like other inflammatory conditions, is related to tissue destruction, cell death and the associated presence of endogenous TLR ligands is a common feature in synovium of patients. Several examples have been described of damage associated endogenous TLR ligands present in synovium, including HMGB1, heat shock proteins, tenascin c, and fibronectin (Gondokaryono et al., 2007; Martin et al., 2003; Midwood et al., 2009; Pullerits et al., 2003; Taniguchi et al., 2003).

These endogenous ligands are thought to contribute to the chronicity of inflammation, as they can activate TLRs, inducing an inflammatory response, further tissue and cellular damage, and thereby the sustained release of damage associated TLR ligands.

Next to damage-associated TLR ligands, cell death can also lead to release of PAD enzymes into the extracellular environment, leading to generation of citrullinated proteins, including fibrinogen. Citrullinated fibrinogen, one of the antigens recognized by ACPA, was shown to trigger TLR-4 (Sokolove et al., 2011). Therefore, chronic inflammation is often related to release or generation of TLR ligands, leading to a self-amplifying inflammatory loop (Fig. 1).

1.3. T helper cells

The strong genetic association of the HLA region with disease susceptibility suggests the involvement of T helper cells in the etiology of rheumatoid arthritis. The association to HLA-DR alleles is not completely understood, but is specifically related to the ACPA response and could therefore be attributed to the helper function of T cells by which they can drive autoantibody responses by B cells (van der Helm-van Mil et al., 2006).

However, T cells themselves may also exert pathogenic effects, for example through their production of cytokines. Initially, Th1 cells, producing IFNγ and TNFα were thought to drive the immune response in rheumatoid arthritis. Since discovery of a wide variety

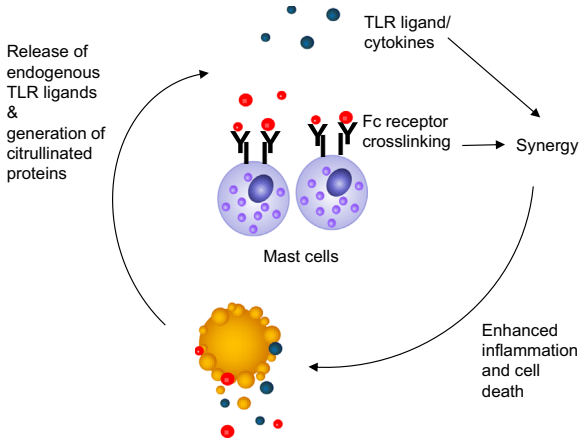

Fig. 1. Chronic inflammation in rheumatoid arthritis is amplified by mast cells. Damage associated Toll Like Receptor (TLR) ligands, cytokines and citrullinated proteins are all implicated in rheumatoid arthritis pathogenesis and are released upon inflammation, in particular in association with cell death. Both have been shown to activate mast cells: citrullinated proteins can form immune complexes with ACPA autoantibodies, and activate mast cells through Fcγ receptors; endogenous ligands can activate mast cells through TLRs; various cytokines can activate mast cells. In the environment of the inflamed joint, all of these triggers are present at the same time, and together lead to synergy in mast cell activation. This synergy leads to enhanced tissue inflammation, in particular neutrophil influx, leading to cell death in the tissue. This cell death can lead to an amplification loop by generating more endogenous TLR ligands and citrullinated proteins.