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THE INVOLVEMENT OF T- AND B-LYMPHOCYTES IN THE PATHOGENESIS AND PROGESSION OF OSTEOARTHRITIS AND OSTEOMYELITIS

Osteoarthritis is the most common joint disorder and a major cause of disability with a major socio-economic impact. In these circumstances is very important to understand its pathogenesis. Although previous research focused primarily on changes in the articular cartilage, more recent studies have highlighted the importance of the subchondral bone, synovium, menisci, ligaments, periarticular muscles and nerves. Now osteoarthritis is viewed as a multifactorial disease affecting the whole joint. Normal adult articular cartilage is made up of extracellular matrix (water, collagen, proteoglycans and a very small component of calcium salt) and chondrocytes (Goldring and Marcu, 2009). The turnover rate of collagen is relatively slow, whereas proteoglycan turnover is rapid (Mow *et al., 2005*). The normal turnover of this matrix components is mediated by the chondrocytes, which synthetize these components and the proteolytic enzymes responsible for their breakdown. Chondrocytes are, in turn, influenced by a number of factors, including polypeptide growth factors and cytokines, structural and physical stimuli and even the components of the matrix itself (Wise, 2010). Osteoarthritis result from failure of chondrocytes to maintain homeostasis between synthesis and degradation of these extracellular matrix components (Heijink *et al*., 2012). It is not known what initiates the imbalance between the degradation and the repair of cartilage.

Trauma causing a microfracture or inflammation causing a slight increase in enzymatic activity may allow the formation of ”wear” particles, which could be then engulfed by resident macrophages (Wang, 2013). At some point in time, the production of these ”wear” particles overwhelms the ability of the system to eliminate them and they become mediators of inflammation, stimulating the chondrocyte to release degradative enzymes. Molecules from breakdown of collagen and proteoglycan, also taken up by synovial macrophages, cause release of proinflammatory cytokines, like TNFα, IL-1 and IL-6. These cytokines can bind to chondrocyte receptors leading to further release of metalloproteinases and inhibition of type II collagen production, thus increasing cartilage degradation (Stannus *et al.,* 2010). This disruption of homeostasis results in increased water content and decreased proteoglycan content of the extracellular matrix, weakening of the collagen network due to decreased synthesis of type II collagen and increased breakdown of pre-existing collagen (Buckwalter *et al.,* 2005). Furthermore, there is increased apoptosis of chondrocytes. Osteoarthritic cartilage is characterized by an increase in anabolic and catabolic activity. At first, compensatory mechanisms such as increased synthesis of matrix molecules (collagen, proteoglycans and hyaluronate) and proliferation of chondrocytes in the deeper layers of the cartilage, are able to maintain the integrity of the articular cartilage, but in the end loss of chondrocytes and changes in extracellular matrix predominate and osteoarthritic changes develop.

Initial degenerative changes in the articular cartilage lead to cartilage softening, fibrillation zone of the superficial layers, fissuring and diminished cartilage thickness, but these changes become more pronounced with time, when articular cartilage thins to total destruction, eventually leaving the underlying subchondral bone plate completely exposed. All these changes in the articular cartilage are referred to as chondropathy.

Although osteoarthritis (OA) has been traditionally regarded as a non-inflammatory disease, reports increasingly suggest that it is inflammatory, at least in certain patients. OA patients often exhibit inflammatory infiltration of synovial membranes by macrophages, T cells, mast cells, B cells, plasma cells, natural killer cells, dendritic cells, granulocytes, etc. Although previous reviews have summarized the knowledge of inflammation in the pathogenesis of OA, as far as we know, no report review our current understanding about T cells, especially, each T cell subtype, in the biology of OA. This review highlights the current understanding of the role of T cells in the pathogenesis of OA, with attention to Th1 cells, Th2 cells, Th9 cells, Th17 cells, Th22 cells, regulatory T cells, follicular helper T cells, cytotoxic T cells, T memory cells, and even unconventional T cells (e.g., γδ T cells and cluster of differentiation 1 restricted T cells). The findings highlight the importance of T cells to the development and progression of OA and suggest new therapeutic approaches for OA patients based on the manipulation of T-cell responses.

T Cells and OA

Analysis of enzyme-linked immunosorbent assay (ELISA) data has shown that compared with age-matched healthy controls, patients with OA show higher levels of the soluble form of CD4 (sCD4) in their serum. This suggests that peripheral T helper (Th) cells are involved in the pathogenesis of OA . Similarly, when stimulated with phorbol myristate acetate (PMA) and ionomycin, peripheral mononuclear cells from OA patients showed a higher expression of CD4 and CD8 markers than their counterparts from healthy controls . Indeed, the ratio of CD4+/CD8+ in the blood of OA patients is higher than that in the blood of healthy controls, although healthy controls and OA patients have fairly similar numbers of CD4+ and CD8+ T cells in their blood . Further evidence of the involvement of peripheral T cells in the pathogenesis of OA was provided by the discovery that the response to autologous chondrocytes of peripheral T cells isolated from OA patients is greater than of peripheral T cells isolated from controls and that this response is partially blocked by antibodies against human leukocyte antigen (HLA) classes I and II, CD4, and CD8 . Interestingly, T cells in a subset of OA patients were found to recognize the peptides representing amino acid regions 16–39 and 263–282 of human cartilage proteoglycan aggrecan (PG), and peripheral blood mononuclear cells from these PG-reactive OA patients showed an increased production of pro-inflammatory cytokines/chemokines in response to PG peptide stimulation. Based on these compelling findings, the autoimmune responses of peripheral T cells may aid understanding of immune-mediated mechanisms in OA.

Enzyme-linked immunosorbent assay analysis revealed higher levels of sCD4 not only in the peripheral blood but also in the synovial fluid of patients with OA, compared with age-matched healthy controls, which suggests that Th cells in the synovial fluid are involved in the pathogenesis of OA. When stimulated with PMA and ionomycin, mononuclear cells from the synovial fluid of OA patients showed a high expression of CD4 and CD8 markers. These compelling results suggested that T cells in the synovial fluid are associated with the pathogenesis of OA. This conclusion was supported by subsequent investigations. For example, the percentage of T cells in the synovial fluid of OA patients was found to be significantly higher than that in their peripheral blood, and T cells in the synovial fluid of OA patients expressed class II HLA (an indicator of activated T cells). The percentages of CD4+ and CD8+ cells in the synovial fluid of OA patients were even similar to those found in RA patients.

T cells are the major constituents of synovial infiltrates in the membranes of OA patients, and both CD4+ T cells and CD8+ T cells have been found within synovial aggregates. For example, synovial tissue extracted from OA patients displayed perivascular CD3+ T cell infiltration at an early stage. Similarly, using immunohistochemical analysis, CD3+, CD4+, and CD8+ T cells were detected predominantly in the sublining layer and more limitedly in the deep layer of the synovium of patients with OA, whereas the presence of CD4+ T cells in the synovial sublining layer was detected more strongly in OA patients than in normal subjects (Nakamura *et al.,* 2002). CD4+ T cells were found to be predominant among the T-cell infiltrates in the synovial tissue, and the number of CD4+ T cells was higher in the synovial sublining layer of patients with OA than in that of normal subjects. Indeed, the medial synovium of patients with knee OA has been shown to contain more CD4+ T cells than the lateral synovium. Interestingly, synovial aggregates from OA patients express CD80, an inducible costimulatory ligand involved in T-cell activation, suggesting that synovial aggregates in OA patients are areas of antigen recognition and T-cell activation. Similarly, researchers investigating 30 patients with OA found CD3+ T cell aggregates in the synovial membrane in 65% of the patients, and the activation antigens CD69, CD25, CD38, CD43, CD45RO, and HLA class II were also found in the synovial membrane. In addition, HLA-antigen D-related (DR)-expressing T cells were found in the synovial membranes of OA patients using immunohistochemical analysis, although to a lesser degree than in RA patients. The conclusion that activated T cells are aggregated in the synovial membranes of OA patients was further supported by the discovery that virtually all T cells in OA joints express activation markers, such as HLA-DR and CD69 (Yamada *et al*., 2011). Interestingly, OA patients older than 75 have higher percentages of CD3+, CD4+, and CD8+ cells in their synovial membranes than OA patients younger than 75 (Pawlowska *et al*., 2011). This may suggest that age is among the risk factors for OA.

Collectively, significant abnormalities in the T-cell profile have been found in the peripheral blood, synovial fluid, and synovial membranes of OA patients. Based on these findings, T cells are assumed to be associated with the pathogenesis of OA.

(OA) is regarded as a prevalent cause of morbidity and disability worldwide. OA shows many disease characteristics, such as cartilage degradation, moderate synovial inflammation, pain, alteration of bony structure, and impaired mobility. However, despite the severity of the disease, relatively little is known about its exact etiology. Recent compelling investigations have attributed the onset of OA to various person-level factors such as age, sex, obesity, and diet and joint-level factors such as injury, malalignment, and abnormal joint loading. Although more and more researchers have recently presented hypotheses concerning the involvement of these factors in OA, especially for person-level factors, few of their hypotheses have been demonstrated experimentally, and some have even been challenged by the latest observational studies and clinical trials.

Of the several factors potentially involved in the pathogenesis of OA, T cell-mediated immune responses and their influence on the biology of OA are the focus of this review. The scientific community once understood OA to be induced by mechanical stress in the form of cartilage destruction, with minimal if any involvement of immune responses. Thus, OA was regarded as a non-inflammatory disease, in contrast with rheumatoid arthritis (RA), an inflammatory disease. However, recent studies suggest that at least in certain patients, OA is an inflammatory disease; patients have frequently been found to exhibit inflammatory infiltration of synovial membranes. Most recent studies have shown that the number of inflammatory cells in the synovial tissue is lower in patients with OA than in patients with RA, but higher than that in healthy subjects. Indeed, little difference has been found in the percentages of T cells, B cells, and natural killer cells in the peripheral blood between patients with OA and RA (Leheita *et al.*, 2005) reflected on the similarity of the immune cell profiles of RA and OA and suggested that abnormalities in T cells may also contribute to the pathogenesis of OA. Further experiments indicated that inflammation in OA is anatomically restricted and varies in intensity. The synovial membranes in regions rimming the cartilage of OA patients, which contain T cells bordered by B lymphocytes and plasma cells, showed a pronounced inflammatory response. In contrast, only a few infiltrating lymphocytes were observed in the synovial membranes taken from macroscopically non-inflamed areas in OA patients. This may explain the suggestion made by some researchers that immune responses are not involved in the pathogenesis of OA. When synovial samples from patients with knee OA were analyzed, the synovial lining cells showed strong immunoreactivity and phagocytic potential with cluster of differentiation (CD) 68 antibodies. These findings suggested that macrophages may be associated with the pathogenesis of knee OA. Of 20 osteoarthritic synovial membranes, 5 showed lymphoid follicles containing T cells, B cells, and macrophages, and 10 (including the latter five) displayed a diffuse cellular infiltrate containing T and B cells, macrophages, and granulocytes. These results suggested that B cells and granulocytes may also be involved in the pathogenesis of knee OA.

To date, various immune cells have been identified in the synovial membranes of OA patients, such as macrophages, T cells, mast cells, B cells, plasma cells, natural killer cells, dendritic cells, and granulocytes. For a detailed description of the infiltration of synovial tissues by immune cells, a recent review of this subject should be consulted. Of these inflammatory cells, macrophages and T cells most abundantly infiltrate the synovial tissues of OA patients. For example, macrophages represent approximately 65% of the immune cells that infiltrate the synovial tissues of patients with OA, and T cells make up 22% of the infiltrate. Although previous reviews have summarized the knowledge of inflammation in the pathogenesis of OA, as far as we know, no report reviews our current understanding about T cells, especially, each T cell subtype, in the biology of OA (Sakkas and Platsoucas, 2002). More importantly, the scientific community has recently contributed to the growing literature on the involvement of T cells in the pathogenesis of OA with some interesting findings regarding the alteration of T cells during OA. Thus, this review focuses on our current understanding of the significance of T cells to OA biology.



**The involvement of T cells in the pathogenesis of osteoarthritis (OA)**. T cells, including the T helper (Th) cells, cytotoxic T cells, and T memory (Tm) cells, have critical importance in the pathogenesis of OA (++). The involvement of unconventional T cells in the pathogenesis of OA is not shown here. Within T helper (Th) cells, Th1 cells, Th9 cells, Th17 cells, and follicular helper T (Tfh) cells increase in the peripheral blood, synovial fluid, or synovial membranes of OA patients (++). The numbers of cytotoxic T cells and Tm cells also increase in the OA. However, the numbers of Th2 cells and Th22 cells show limited alteration in the pathogenesis of OA (−), but the number of Treg cells decrease during the OA (−−).

Follicular helper T cells, located in the follicles of lymphoid tissue, induce B cells to produce immunoglobulins (Ueno *et al*., 2015). Tfh cells express various distinguishing genes, such as CXCR5, PD-1, ICOS, CD40L, Bcl-6, and IL-21 (Crotty, 2011). Increasing evidence has been provided for the influence of Tfh cells on the severity of autoimmune diseases, such as SLE and RA. For example, the number of circulating Tfh cells (CXCR5+ICOS+CD4+ cells or CXCR5+PD-1+CD4+ cells) has been shown to increase in a subset of SLE patients in line with the diversity and concentration of autoantibodies and SLE severity (Simpson *et al., 2010*). Similarly, immunohistochemistry analysis has revealed specific staining for CD4, CXCR5, and ICOS on infiltrating immune cells in the synovial tissues of RA patients, and the presence of Tfh cells (CD4+CXCR5+ICOS+ T cells) in the synovial tissues of RA patients has been verified using both triple-fluorescence immunostaining and confocal laser scanning (Chu *et al.,* 2013). This study provided evidence of the presence of Tfh cells in both SLE and RA patients, indicating the potentially important roles played by Tfh cells in the pathogenesis and progression of both diseases. However, the results of immunohistochemistry analysis, triple-fluorescence immunostaining, and confocal laser scanning revealed that Tfh cells are absent from the synovial tissues of OA patients (Chu et al., 2013). Yet, a recent investigation demonstrated the importance of Tfh cells to the pathogenesis and progression of OA. In the latter study, the frequency of ICOS+, PD-1+, and IL-21+ CXCR5+CD4+ T cells in the peripheral blood of 40 patients with OA and 13 healthy controls was examined by flow cytometry, and the concentration of serum IL–21 was also determined. Compared with the healthy controls, the OA patients showed higher percentages of CXCR5+CD4+, PD-1+CXCR5+CD4+, ICOS+CXCR5+CD4+, and IL-21+CXCR5+CD4+ T cells (Shan et al., 2017) also found that OA patients exhibited higher levels of serum IL-21 than healthy controls and, even more importantly, that the expression of IL-21+Tfh cells in OA patients was positively correlated with the disease activity of OA (Shan et al., 2017). The latter study suggests that Tfh cells play a critical role in the pathogenesis and progression of OA. However, further well-designed research is needed to characterize Tfh cell profile in the peripheral blood, synovial fluid, and synovial membranes of OA patients.

Cytotoxic T Cells and OA

The peripheral blood of OA patients has been analyzed using flow cytometry, revealing that patients with OA have significantly fewer CD8+ T cells and a higher CD4+:CD8+ ratio than healthy subjects (Kuryliszyn-Moskal *et al*., 1995). However, patients with OA have normal proportions of CD8+CD45RA+, CD8+CD29+, and CD8+S6F1+ cells in both their peripheral blood and their synovial fluid. These results indicate the alteration of peripheral CD8+ T cells in OA patients. Although CD8+ T cells can be found in the synovial membranes of OA patients, the major component of the T-cell infiltrate cannot. Most of the T cells found in the synovial membranes of patients with OA are helper T cells, whereas cytotoxic T cells occur sparsely in patients with OA. Similarly, fewer CD8+ T cells than CD4+ T cells have been found in the lining, the sublining, and even the deep layer of the synovium of patients with OA. In addition, although both CD4+ and CD8+ T cells have been found in the synovial aggregates of OA patients, the aggregates contain a larger proportion of CD4+ T cells than of CD8+ T cells, and the CD8+ T cells are often located toward the periphery of the aggregates. CD8+ T cells play an important role in the pathogenesis of OA, although they are not the predominant T-cell type found in the synovial aggregates of OA patients. In mice with ACLT-induced OA, CD8+ T cells were activated once OA had been initiated, and the percentage of activated CD8+ T cells was significantly higher in the ACLT group than in the sham group during OA progression (Hsieh *et al*., 2013). In addition, the number of CD8+ T cells expressing tissue inhibitor of metalloproteinase-1 (TIMP-1) was found to be correlated with OA severity and inhibiting the expression of TIMP-1 in the joints retarded the progression of OA (Hsieh et al., 2013). Cartilage degeneration occurred more slowly in CD8+ T cell knockout mice than in wild-type mice ([87](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5371609/#B87)).

In summary, a significant alteration to CD8+ T cells has been observed in the peripheral blood, the synovial fluid, and the synovial membranes, and CD8+ T cells have been found to significantly shape the pathogenesis of OA, although they do not play the most important role in the process.

T Memory (Tm) Cells and OA

Once activated, most T cells undergo apoptosis; however, a minority persist as Tm cells. An increasing number of researchers have begun to investigate the profile of Tm cells in the pathogenesis of OA. For example, although healthy individuals showed no difference in the percentages of CD45RO+CD4+ T cells and CD45RA+CD4+ T cells in the peripheral blood, more CD45RO+ cells than CD45RA+ cells were found in the peripheral blood of patients with OA (Ota *et al*., 1997). In patients with OA, the majority of CD4+ T cells in the synovial fluid and synovial tissue are CD45RO+ and CD45RA−, suggesting that an accumulation of CD45RO+ memory CD4+ T cells is a generalized phenomenon in OA joints (Ota et al., 1997). Similarly, a study with 25 OA patients and 13 healthy controls revealed that the number of circulating CD4+CD45RO+ T cells was significantly higher in patients with OA than in healthy controls. Other evidence for the possible involvement of Tm cells in the pathogenesis of OA includes the detection of the regulated on activation, normal T cell expressed, and secreted chemokine (a potent chemoattractant for leukocytes, such as CD45RO+ memory T cells) and CD29 (a 1 integrin expressed by Tm cells) in the synovial fluid of OA patients (Volin *et al.,* 1998).

In summary, CD45RO+ memory CD4+ T cells seem to be critical to the biology of OA, yet their exact roles in the pathogenesis of OA have yet to be determined.

Unconventional T Cells and OA

Recent investigations have also highlighted the involvement of unconventional T cells in the pathogenesis of OA. For example, more and more evidence has been provided that γδ T cells are involved in the pathogenesis of RA. For example, the number of γδ T cells has been found to increase in the synovial membranes of RA patients (Pisano *et al.,* 1981) and γδ T cells in the synovial membranes have more and/or more avid Fc receptors for immunoglobulin G IgG in patients with RA compared with controls (Pisano *et al.,* 1981). Further research has shown that the majority of synovial γδ T cells in RA patients do not express Vγ9, Vδ2, or Vδ1-Jγδ1 (Alonso *et al.,* 1991). However, most recent studies have indicated that the number of γδ T cells in the synovial membranes of patients with OA does not increase (Alonso et al., 1991). Immunohistochemical staining of synovial tissue with early-stage OA shows T-cell infiltration in the perivascular area, with the clonality of restricted T cell receptor usage in the V beta chain, which also indicates the minimal alteration of γδ T cells in OA patients. Recent studies have shown that the synovial membranes of OA patients express CD1, which presents non-protein antigens to NKT cells, suggesting that CD1-restricted T cells may play a role in the pathogenesis of OA.

Overall, although numerous studies of the involvement of conventional T cells in OA have been conducted, it will be useful to determine the importance to OA of unconventional T cells such as CD1-restricted T cells, MR1-restricted mucosal-associated invariant T cells, major histocompatibility complex class Ib-reactive T cells, and γδ T cells.

B-lymphocytes play several critical roles in the pathogenesis of rheumatoid arthritis. They are the source of the rheumatoid factors and anticitrullinated protein antibodies, which contribute to immune complex formation and complement activation in the joints. B cells are also very efficient antigen-presenting cells, and can contribute to T cell activation through expression of costimulatory molecules. B cells both respond to and produce the chemokines and cytokines that promote leukocyte infiltration into the joints, formation of ectopic lymphoid structures, angiogenesis, and synovial hyperplasia. The success of B cell depletion therapy in rheumatoid arthritis may depend on disruption of all these diverse functions.

IgG autoantibodies and immune complexes have long been recognized as potent pathologic triggers of inflammatory responses. Early hypotheses regarding the pathogenesis of rheumatoid arthritis (RA) were molded by experimental models of immune complex disease. IgG aggregates are abundant in RA synovial fluids, and can trigger complement activation. Hence, it seemed logical that tissue damage in RA was attributable to the local deposition of immune complexes.

Rheumatoid factors (RFs), which are autoantibodies specific for the constant regions of IgG, are detectable in more than 80% of RA patients, and may also be present in a 'hidden' or complexed form in the synovial fluids of some seronegative patients. RFs efficiently fix and activate complement in vitro by the classic pathway (Cassatella *et al.,* 2014). In vivo turnover studies of radio tagged complement proteins in seropositive RA patients demonstrated that, compared with control individuals, complement consumption was greatly accelerated, especially at the extravascular sites of inflammation (Pigenet *et al.,* 2015). Consistent with the notion that immune complex formation was maximal at the synovial sites of inflammation, complement activation was shown to be much greater in RA synovial fluid than in blood (Pigenet *et al.,* 2015). Levels of C4 fragments at these sites also correlated with titers of IgM RFs.

Infiltrating leukocytes are known to be recruited by the downstream products of complement activation, especially the soluble anaphylatoxin C5a, with subsequent enlistment of other components of the membrane attack complex (Luo *et al.,* 2017). Flares of clinical activity in RA correlate with increased levels of RF secreting cells, which are especially prevalent in the bone marrow and synovial fluid of RA patients (Feijt *et al.,* 2012).

IgM RFs have been reported to account for more than 10% of local plasma cells in RA synovia. However, infusions of RF into healthy individuals causes neither sustained nor transient synovitis, indicating that RF autoantibodies by themselves are not pathogenic. Nevertheless, IgM-RF-containing immune complexes may also include IgG antibodies and unidentified peptides, which could derive from self or exogenous antigens. In addition, the recently resolved crystallographic structure of a human IgM RF–Fc co-complex revealed that contacts with IgG antigen involved only the periphery of the antigen-binding cleft of the autoantibody. These findings may indicate that RA RF is capable of binding IgG as well as another self or foreign antigen. Thus, although RF alone is not proinflammatory, RF associated with immune complexes can enhance local inflammatory processes, and there is compelling clinical evidence that RFs contribute to extra-articular disease.

Antigen-presenting function of B cells

In addition to being the precursors of antibody-secreting plasma cells, the B cells in RA can play a critical role in the afferent arm of the immune response. Thus, B cells can act as highly efficient antigen-presenting cells (APCs), supporting the activation of autoreactive T cells. In fact, by virtue of the high affinity of a specific membrane-associated immunoglobulin for antigen, an antigen-specific B cell can take up, process, and present peptides from nominal antigen with 1000-fold or greater efficiency than a 'professional' APC. In addition, activated B cells can synthesize cytokines and membrane-associated molecules that provide nonspecific help to adjacent T cells.

Major physiologic functions of B lymphocytes

Precursors of antibody producing plasma cells

Provide noncognate help for T cell activation

Efficient antigen-presenting cells, especially for recall antigens

Produce cytokines (i.e. IL-4 and IL-10) that support the survival other mononuclear cells

Generate and respond to chemotactic factors responsible for leukocyte migration and development of granulation tissue

Sustain immunologic memory

Strong experimental support for a central role of B cells in RA pathogenesis, independent of antibody formation, came from studies of human synovium/SCID mouse chimeras. Those studies confirmed that the T cell activation is B cell dependent, in that targeted deletion of B cells impaired local T cell responsiveness, and APCs other than B cells could not substitute for the maintenance of T cell activation.

Role of B cells in murine models of rheumatoid arthritis

Following the development of methods for introduction of transgenes and for targeted gene disruption, in vivo murine models have been developed that have enabled a re-evaluation of the role of B cells in arthritis. The KRN/NOD murine model has been particularly revealing, because in these mice there is complete penetrance of a genetically determined disease process that results in severe distal joint inflammation, which emulates key features of RA. Moreover, development of the disease involves the coordinated functions of both B cells and T cells, because infusion of nondepleting antibody to CD4 blocks disease, and mice devoid of B cells also do not develop disease. A pathogenic role for IgG autoantibodies to glucose-6-phosphate isomerase (GPI) has been documented in the KRN/NOD model; it was found that infusions of these autoantibodies into otherwise healthy mice rapidly led to the development of synovitis. However, arthritis was not induced by introduction of preformed anti-GPI antibody–antigen complexes, which suggested that joint disease can result when autoantibodies, produced either locally or systemically, interact with antigens on synovial surfaces to develop immune complexes in situ. These locally formed immune complexes were shown to be proinflammatory only if they involve antibodies to two or more epitopes, and the more diverse the antibody response, the more efficient the recruitment of proinflammatory factors, suggesting that a complex IgG autoantigen lattice is required for the recruitment of downstream inflammatory effectors.

Studies in the KRN/NOD model have also enabled a closer dissection of the role of complement in the development of immune complex mediated synovitis. Although anti-GPI antibodies are prevalent in the circulation, disease is limited to the joints, probably because only articular immune complexes are efficient at fixing complement. C4-deficient KRN/NOD mice develop arthritis of the same severity as do wild-type mice, whereas animals deficient in factor B of the alternative complement pathway develop attenuated disease or no arthritis at all. In addition, a partial dependence on C3 was also demonstrated, which is consistent with the known role of C3 in the stabilization of immune complexes. These findings have led to a revision of the earlier notion that IgG immune complexes trigger inflammation primarily by engagement of the classical pathway of complement activation, because these murine studies indicated that disease initiation instead may involve the alternative pathway.

Although interactions between immune complexes and cellular receptors for the Fc regions of IgG (FcγR) were not considered in earlier clinical investigations of RA, the recent characterization of these receptors and the availability of relevant murine model systems has permitted a thorough examination of their impact on pathogenesis. The three classes of Fcγ cell surface receptors, isolated based on their capacity to bind IgG-containing immune complex, are heterogeneous in their binding specificities for IgG1–IgG4, and their intracellular signaling motifs that can either activate or inhibit cellular effector functions. Although mice with deficiencies in complement components typically exhibit attenuated immune complex mediated disease in relevant murine models, the loss of activating FcγRIII completely ablates arthritis development (Harris and Vaughan, 1961) Connecting these model systems to clinical disease, in vitro blockade of FcγRIIIA on human macrophages was recently shown to prevent the release of tumor necrosis factor (TNF)-α and induction of IL-1α in human macrophages. FcγRIII may be an especially important mediator of immune complex induced tissue damage in RA, because of the size and composition of immune complexes that arise at sites of disease (discussed by Edwards and co workers. In more recent studies, C5a, acting through the C5a receptor, was shown to exacerbate immune complex induced inflammatory disease by altering the ratio of activating to inhibitory FcγR on macrophages. These studies demonstrated a direct link between the C5a chemoattractant and FcγR related mechanisms responsible for immune complex triggered inflammatory responses.

These investigations of murine models of RA have led to a revision of our understanding of the role of secreted autoantibodies in RA. Complement alone may be inadequate to sustain chronic inflammatory responses to immune complex deposition, because stimulatory and inhibitory FcγR may in fact be the primary regulators of subsequent immune responses. The host response to immune complex functions in the joints is critically dependent on interactions with cell surface FcγR on B cells and macrophages.

Immune complexes and mast cells

Mast cells are prominent in the synovial infiltrates of many RA patients, and these tissue associated infiltrating cells express membrane associated FcR for IgE and IgG, which enable triggering resulting from antigen-specific (and perhaps nonspecific) immunoglobulin cross-linking. In murine models of immune complex disease, the mast cell has been shown to play a central role in immune complex mediated joint inflammation (Maccioni *et al*., 2002). Mast cells triggered by immune complexes produce proinflammatory cytokines and proteolytic enzymes at sites of cartilage erosions (Mahmood *et al.,* 2002). The mast cells are also major sources of the vasoactive and chemotactic factors that facilitate the recruitment of other leukocytes to the synovial tissues. KRN/NOD mice that lack mast cells are resistant to inflammatory and erosive arthritis induced by arthritogenic serum. Along with macrophages, mast cells can release TNF-α and IL-1. For these reasons, the mast cell is now appreciated to be a cellular link between B cells, autoantibodies, complement, and other inflammatory mediators that contribute to erosive arthritis.

Anti-GPI antibodies and rheumatoid arthritis

Based on the unexpected discovery that antibodies to GPI can induce synovitis in healthy mice, several groups have looked for a role for these autoantibodies in clinical disease. GPI is a ubiquitous enzyme that is essential for glucose metabolism in all cell types, and it therefore cannot represent a tissue-specific antigen recognized as part of an autoimmune disease that is limited to the joints. A more likely scenario is that increased local cell turnover results in the deposition of GPI along joint surfaces, where it may be recognized by autoantibodies that enter from the circulation. Although Schaller and co workers reported increased anti-GPI antibody titers in 64% of 69 RA patients, but not in patients with Lyme disease or Sjögren's syndrome, these findings were not confirmed in subsequent reports. In a recent flurry of studies, only a small minority of RA patients had detectable levels of autoantibodies to GPI, and there were no significant differences from patients with other types of joint diseases. However, it remains a possibility that anti-GPI antibodies may be more common in RA patients with extra-articular disease, and especially in patients with Felty's syndrome, which were highly represented in the first reported clinical survey.

Antibodies against citrulline-modified proteins

Many RA patients have circulating antibodies to autoantigens other than IgG, including type II collagen, heat shock proteins, proteoglycans, cartilage link protein, and heavy chain binding proteins. In some cases T cell reactivity to the same antigens was demonstrated by in vitro proliferation assays. In certain instances experimental immunization with the antigens in complete Freund's adjuvant can cause arthritis in rodent models. However, immune responses to each of these antigens have been detected in only a minority of patients, and a causative role in clinical disease has not been firmly established. Therefore, at best, such joint-specific autoantibodies cannot account for chronic inflammatory arthritis in most RA patients.

More prominent in RA are IgG antibodies to citrulline-modified peptides and proteins (CCP). Citrullination represents a post-translational modification due to the enzymatic deamination of peptidyl arginine to peptidyl citrulline. It has been shown that citrulline is the essential antigen epitope recognized by anti-CCP antibodies, antiperinuclear antibodies, as well as antibodies to keratin, filaggrin, and Sa. In fact, one extensive study concluded that although RF may be a more sensitive test for RA, detection of anti-CCP antibodies is more than 90% specific for the diagnosis of RA. Hence, the available evidence supports a role for serologic testing for anti-CCP antibodies as an aid in the diagnosis of RA, especially at early stages of disease (Schubert *et al*., 2002).

Although the biologic significance of anti-CCP antibodies is unclear, citrullination may be a byproduct of abnormal protein metabolism occurring at in vivo sites of increased or abnormal apoptosis. The B lymphocytes from RA patients are resistant to certain apoptotic stimuli, which may reflect prosurvival signals delivered from synovial or bone marrow stromal cells. Notably, increased production of citrullinated peptide autoantibodies has been demonstrated in two murine model systems of autoimmunity with abnormalities in B cell apoptosis, whereas anti-CCP responses were not associated with other autoimmune models that included the classical collagen-induced arthritis system. These findings may suggest that the generation of autoantibodies to citrulline related neoantigens could be closely linked to mechanisms responsible for impaired lymphocyte clonal regulation. Citrullination of proteins may also have the potential to contribute directly to the autoimmune response. An unexpected mechanistic linkage was found in studies of mice transgenic for the human HLA-DRB1\*0401 MHC class II molecule, which contains the 'shared epitope' – a well studied genetic susceptibility factor for RA. In vitro incubation of transgenic B cells and macrophages with citrulline-containing peptides resulted in enhanced peptide side chain interactions with the shared epitope that significantly increased peptide MHC affinity.

Ectopic lymphoid tissue in rheumatoid arthritis

About 60% or more of the synovial samples from RA patients have infiltrates of B and T lymphocytes. Three separate patterns of infiltrates have been described: diffuse lymphocytic infiltrates with interdigitating dendritic cells and variable amounts of B cells; aggregates of infiltrating B and T cells in more substantial numbers, associated with interdigitating dendritic cells in disorganized groupings; and T cells and B lymphocytes clustered in aggregates arrayed around interdigitating dendritic cells and associated with follicular dendritic cell networks. In this latter pattern, which is present in less than one-third of patients, the synovial cellular infiltrates appear to be organized into distinct B cell follicle-like structures in close spatial relationship to CD4+ T cells and CD8+T cells. In general, these histologic features are similar to the germinal center (GC) reactions that arise in peripheral lymphoid tissues during antigen-specific responses after immunization (Goldbach-Mansky *et al*., 2000).

The affected joints of patients with ankylosing spondylitis have also been shown at times to harbor GC-like aggregates. Even the synovia from osteoarthritic joints can occasionally contain infiltrates of activated B cells and plasma cells exhibiting clonally related antibody gene sequences. In addition, lymphotoxin-β (LT-1β2), which is produced by activated T cells, may be a downstream effector that is required for the development of primary B cell follicles in the synovial infiltrates. Rheumatoid synovial tissues have also unexpectedly been found to be rich sources of CXCL12 (also termed stromal cell derived factor [SDF]-1). In fact, SDF-1 produced by fibroblast-like synoviocytes has been shown to contribute to the resistance of B cells to apoptosis, which supports an earlier hypothesis that specialized synovial 'nurse-like cells' peculiar to RA synovium mediate homing and survival of B cells. In recent studies plasma cells have also been shown to migrate toward gradients of SDF-1, CXCL9 (monokine induced by IFN-γ), CXCL10 (IFN-γ-inducible protein 10), and CXCL11 (IFN-inducible T cell α chemoattractant). SDF-1, as well as IL-5, IL-6, TNF-α, and ligands for CD44, can also prolong the longevity of plasma cells. In addition, the TNF-α family member B lymphocyte stimulator (BLyS, also called Baff) has also recently been detected at high levels in rheumatoid synovial fluid, suggesting that this prosurvival factor can also be locally produced in inflamed joints.

The dysregulated expression of cytokines and costimulatory molecules explains the reported accumulation in one-third of RA samples of an unusual subpopulation of peripheral B cells with a restricted immunoglobulin variable region gene repertoire that coexpress conventional light chains and the surrogate light chain of pre-B cells. Such B lineage cells have been postulated to be promiscuous in antigen presentation, and thus could present diverse autoantigens. This topic is still highly controversial because other investigators have not found these B lineage cells in healthy tissues, and have challenged the authenticity of their reported phenotype.

The imprint of the potent chemoattractive activating and antiapoptotic factors described above may largely explain the skewed distribution of the B lymphoid cells that accumulate in the synovium. The local production of these factors at sites of inflammation in RA joints may serve as beacons to foster B cell accumulation, proliferation, and differentiation. An active (auto)antigen driven GC reaction may not be required to explain the development of the ectopic B lymphoid infiltrates in the joints of RA patients.

Recent reports have confirmed the importance of immune complexes in the pathogenesis of RA, and have elucidated additional critical roles for B cells and their immunoglobulin products in self-sustaining chronic inflammatory processes.These findings have contributed to the rationale for the development of targeted therapies that delete B cells or that attenuate the function of secreted and membrane associated factors that contribute to B cell accumulation and survival at sites of disease. However, an appreciation of these diverse potential roles may also predict that the targeted interference with just one B cell antigen or costimulatory molecule may not be sufficient to arrest ongoing disease in all RA patients.

Potential pathologic functions of B lymphocytes in autoimmune disease

Presentation of immune-complexed antigens to autoreactive T cells

Expression of adhesion and other costimulatory molecules that promote T cell activation

Synthesis of chemokines that induce leukocyte infiltration

Production of factors that initiate and sustain angiogenesis and granulation tissue formation

Release of autoantibodies that are directly or indirectly (via immune complex formation) destructive to tissues

Maintenance of a memory response to autoantigens

The role of B cells for the pathogenesis of rheumatoid arthritis (RA) has been debated for a long time. Here we show that chronic inflammation in the affected joints leads to the development of ectopic germinal centers. A micro-environment is established which supports B cell activation and differentiation. Plasma cells may develop which secrete autoantibodies of high affinity directly into the synovial tissue. Antigen/antibody complex formation, the activation of the complement cascade and the stimulation of macrophages may contribute to the destruction of joints. Furthermore, B cells are efficient antigen presenting cells. They seem to play a pivotal role in the activation of synovial T cells and the induction of cytokine secretion. The success of B cell depletion therapy by using the monoclonal antibody Rituximab further emphasized the importance of B cells in the pathogenesis of RA.

OSTEOMYELITIS

Osteomyelitis is an inflammatory bone disease that is caused by an infecting microorganism and leads to progressive bone destruction and loss. The most common causative species are the usually commensal staphylococci, with Staphylococcus aureus and Staphylococcus epidermidis responsible for the majority of cases. Staphylococcal infections are becoming an increasing global concern, partially due to the resistance mechanisms developed by staphylococci to evade the host immune system and antibiotic treatment. In addition to the ability of staphylococci to withstand treatment, surgical intervention in an effort to remove necrotic and infected bone further exacerbates patient impairment. Despite the advances in current health care, osteomyelitis is now a major clinical challenge, with recurrent and persistent infections occurring in approximately 40% of patients. This review aims to provide information about staphylococcus-induced bone infection, covering the clinical presentation and diagnosis of osteomyelitis, pathophysiology and complications of osteomyelitis, and future avenues that are being explored to treat osteomyelitis.

Bone is a dynamic connective tissue that is constantly being remodeled and renewed under the governance of three main bone cells: osteoblasts, osteocytes, and osteoclasts. Osteoblasts are the bone-forming cells, derived from mesenchymal stem cells (MSC) in the bone marrow, and are responsible for producing the main organic extracellular matrix (ECM) components of bone. When osteoblasts are fully mature cells, they produce osteoid—unmineralized organic bone matrix—in the form of a membrane-bound vesicle (Martin *et al.,* 2008). Osteoid consists of collagenous and noncollagenous proteins. Collagen type I makes up 90% of the osteoid, with the remainder comprised of proteins, such as proteoglycans (Mayne *et al.,* 2000) and glycoproteins. Common glycoproteins found in the ECM include fibronectin, osteonectin, osteopontin, bone sialoprotein, and osteocalcin (Blaire *et al*., 1978). When osteoblasts generate and fully immerse themselves in ECM, they become osteocytes—terminally differentiated osteoblasts. Osteocytes have been implicated in directing the bone remodeling process through their ability to respond to bone loading and detection of microcracks. Osteoclasts are the bone-resorbing cells, which operate by decalcifying hydroxyapatite and degrading organic ECM. Osteoclasts work in harmony with osteoblasts to retain bone remodeling homeostasis. Notably, an imbalance in the activity between these cells can result in altered bone morphology and pathological bone (Nakamura, 2007). When bone is exposed to the external environment, bone cells and the ECM are ideal colonizing targets of microbes, in particular staphylococci, which have the MSCRAMMs and anchoring proteins to colonize bone (Josse *et al.,* 2015).

Lymphomas have diverse clinical presentations, may affect multiple organ systems, and have been diagnosed across different age groups. Bone involvement is present in 16–20% of patients, and patients with bone involvement often present with pain, mass, fractures, and fever (Unni and Hogendoorn, 2002). These non-specific symptoms can lead physicians to misdiagnose the patients with septic arthritis, osteomyelitis, or primary bone tumors. Histopathological examination is the gold standard for diagnosis; however, in some cases, this type of examination is difficult or impossible. Moreover, the clinical and histopathological distinction between osteomyelitis and malignancy is sometimes difficult, and misdiagnoses have been reported (Cabanela *et al.,* 1974). We report a case of lymphoma that occurred at the hip joint and mimicked osteomyelitis and septic arthritis. A 25-year-old male presented to the emergency department with a one-month history of pain in the right hip, walking difficulty, and fever. On physical examination, he had a high fever (39℃), pallor, and right hip arthralgia with decreased range of motion. The laboratory examination revealed pancytopenia (neutrophils: 500/µL, lymphocytes: 500/µL, blood hemoglobin level: 64 g/L, platelets: 36,000/µL) and elevated serum C-reactive protein (60 mg/L), erythrocyte sedimentation rate (42 mm/hr), lactate dehydrogenase (LDH, 1,928 IU/L), alkaline phosphatase (ALP, 749 IU/L), and gammaglutamyl transferase (GGT, 223 IU/L) levels. Serological tests for hepatotrophic viruses were negative. The pelvic magnetic resonance image (MRI) showed destruction of the right femoral head and edema in the right femoral metaphysis and shaft. We consulted the orthopedics department and initially diagnosed the patient with right femoral osteomyelitis and septic arthritis of the right hip joint. Three sets of blood cultures were drawn, and intravenous ampicillin/sulbactam and ciprofloxacin were started while preparing for orthopedic surgery.

No clinical or laboratory improvement was noted after the first week of treatment, and a peripheral blood smear revealed atypical lymphocytes. A triphasic bone scan scintigraphy showed increased late-phase activities in the frontal and parietal bones, right hip joint, right femoral condyle, right proximal and distal epiphyses of the tibia, and right tarsal bones (Fig. 1). A bone marrow biopsy showed infiltration of T-cell/histiocyte-rich B-cell lymphoma (TC/HRBCL) (Fig. 2A–C), and thoracic and abdominal CT scans identified diffuse pathological lymphadenopathies. The R-CHOP regimen with radiotherapy to the right hip joint was initiated, and the patient's clinical and laboratory findings improved after the first four cycles of R-CHOP treatment. The patient achieved complete remission after eight cycles of R-CHOP treatment; however, the disease relapsed one year later, and the patient died due to septic shock after an ESHAP regimen.

This chapter provides an update on the mechanisms of microbial pathogenesis and the host response to bone infections, with a focus on immune and bone cell interactions during this process. Although humans have been combating microbial pathogens since prehistoric times, infectious disease remains one of our greatest public health challenges. As testimony to the importance of this issue, antibiotic drugs and prophylactic vaccines are considered the first and third greatest scientific achievements of the twentieth century. Despite these major medical advances, one needs to look no further than the recent worldwide pandemic of H1N1 influenza virus infection to understand how vulnerable we remain to pathogenic organisms. Despite the development of superior orthopedic surgical techniques, newer diagnostic tools, and innovative treatments, new problems including multidrug resistance and evolving bacterial virulence allow osteomyelitis to remain a significant challenge in orthopedics. Furthermore, the outcome after currently available treatment is often unsatisfactory, with a therapy failure rate greater than 20%. Recent data suggesting that osteoclastic cells play important roles in immune responses in bone have spawned the new field of osteoimmunology. Thus, a new emphasis has been placed on osteoimmunology to better explain the pathogenesis of bone infections and to derive novel interventions for osteomyelitis.

Osteoimmunology in the context of multiple myeloma is a newly emerging field, and it is clear that interactions between myeloma cells and cells of the immune system are important both in terms of tumor growth and the development of the osteolytic bone disease. Increasing our understanding of the role of the immune system in myeloma bone disease, for example, the effect of the immunosuppression that is found in patients with myeloma will ultimately identify new therapeutic targets for the treatment of myeloma. Current knowledge is limited due to the difficulty of verifying intriguing in vitro observations in appropriate in vivo systems. Immune cells can have both a deleterious and advantageous role in myeloma pathogenesis. Macrophages and T cells, for example, can become altered by the presence of myeloma cells within the bone marrow cavity and act to support further cancer progression; however, the immune system can also be utilized for anticancer therapies. Within a healthy individual, the immune system provides defense mechanisms critical for protecting the body against foreign pathogens as well as tumor formation. The manipulation or stimulation of the body's natural immune system to fight cancer provides an attractive area for therapeutic potential. Emerging cancer research of recent years not only demonstrates genetic alterations to the cancer cells but also to the surrounding microenvironment.

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