**THE INVOLVEMENT OF T AND B LYMPHOCYTES IN THE PATHOGENESIS AND PROGRESSION OF OSTEOMYELITIS AND OSTEOARTHRITIS**

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**1.0 Introduction**

**1.1 Osteomyelitis**

Osteomyelitis is an infection of bone or bone marrow with a propensity for progression, usually caused by pyogenic bacteria or mycobacteria. Osteomyelitis is inflammation of the bone and marrow, but, since it is always caused by an infection, it implies an infection. When an infection develops inside the bone, the immune system will try to kill it. Neutrophils, a type of white blood cell, will be sent to the source of the infection to kill the bacteria or fungus. If the infection takes hold and is not treated, dead neutrophils will accumulate inside the bone, forming an abscess, or pocket of pus. The abscess may block vital blood supplies to the affected bone. In chronic osteomyelitis, the bone may eventually die. Bones are normally resistant to infection, but infection may enter a bone under certain conditions. An infection in the bloodstream, complications of trauma or surgery, or pre-existing conditions, such as diabetes, Reduce the person's ability to resist infection (Bhowmik *et al*., 2018).

Types of Osteomyelitis: It can be subclassified on the basis of the causative organism, the route, duration and anatomic location of the infection. There are three types of osteomyelitis.

1. Acute osteomyelitis, where the bone infection develops within two weeks of an initial infection, injury or the onset of an underlying disease.

2. Sub-acute osteomyelitis, where the bone infection develops within one to two months of an initial infection, injury or onset of an underlying disease.

3. Chronic osteomyelitis, where the bone infection develops two months or more after an initial infection, injury or onset of an underlying disease (Bhowmik *et al*., 2018).

**1.1.1 Pathogenesis of Osteomyelitis**

Osteomyelitis may be caused from hematogenous spread, direct inoculation of microorganisms into bone, or from a contiguous focus of infection. A trivial skin infection may be the source of bacteremia or it may emerge as the result of a more serious infection such as acute or subacute bacterial endocarditis. Injection drug abuse has been linked to hematogenous osteomyelitis involving the long bones or vertebrae (Beronius *et al*., 2001). Hematogenous osteomyelitis usually involves the metaphysis of long bones in children or the vertebral bodies in adults. With hematogenous osteomyelitis, the joint is usually spared from infection in children, unless the metaphysis is intracapsular, as is found at the proximal radius, humerus, or femur (Dahl *et al*., 1998; Trobs *et al*., 1992). The most common causes of direct inoculation osteomyelitis are penetrating injuries and surgical contamination. Contiguous focus osteomyelitis commonly occurs in patients with severe vascular disease.

In general, microorganisms may infect bone through one or more of three basic methods

* Via the bloodstream (haematogeneously) – the most common method (Luqmani *et al*., 2013)
* From nearby areas of infection (as in cellulitis), or
* Penetrating trauma, including iatrogenic causes such as joint replacements or internal fixation of fractures or secondary periapical periodontitis in teeth. (Kumar *et al*., 2007)

The area usually affected when the infection is contracted through the bloodstream is the metaphysis of the bone (Luqmani *et al*., 2013). Once the bone is infected, leukocytes enter the infected area, and, in their attempt to engulf the infectious organisms, release enzymes that lyse the bone. Pus spreads into the bone's blood vessels, impairing their flow, and areas of devitalized infected bone, known as sequestra, form the basis of a chronic infection (Kumar *et al*., 2007). Often, the body will try to create new bone around the area of necrosis. The resulting new bone is often called an involucrum (Kumar *et al*., 2007). On histologic examination, these areas of necrotic bone are the basis for distinguishing between acute osteomyelitis and chronic osteomyelitis. Osteomyelitis is an infective process that encompasses all of the bone (osseous) components, including the bone marrow. When it is chronic, it can lead to bone sclerosis and deformity.

Chronic osteomyelitis may be due to the presence of intracellular bacteria (inside bone cells) (Ellington, 1999). Also, once intracellular, the bacteria are able to escape and invade other bone cells (Ellington, 2003). At this point, the bacteria may be resistant to some antibiotics (Ellington, 2006). These combined facts may explain the chronicity and difficult eradication of this disease, resulting in significant costs and disability, potentially leading to amputation. Intracellular existence of bacteria in osteomyelitis is likely an unrecognized contributing factor to its chronic form.

In infants, the infection can spread to a joint and cause arthritis. In children, large subperiosteal​abscesses can form because the periosteum is loosely attached to the surface of the bone (Kumar *et al*., 2007).

Because of the particulars of their blood supply, the tibia, femur, humerus, vertebra, the maxilla, and the mandibular bodies are especially susceptible to osteomyelitis (King *et al*., 2006). Abscesses of any bone, however, may be precipitated by trauma to the affected area. Many infections are caused by Staphylococcus aureus, a member of the normal flora found on the skin and mucous membranes. In patients with sickle cell disease, the most common causative agent is Salmonella, with a relative incidence more than twice that of S. aureus (Burnett *et al*., 1998).

**1.2 Osteoarthritis**

Osteoarthritis (OA) is a chronic disease and results from damage to articular cartilage induced by a complex interplay of genetic, metabolic, biochemical, and biomechanical factors followed by activation of inflammatory response involving the interaction of cartilage, subchondral bone, and synovium (Creamer and Hochberg, 1997). Many factors- some modifiable- contribute to an increased risk of OA and include obesity, genetics, aging and trauma to the joint. In most patients without a strong genetic predisposition, OA is thought to start as a result of damage to the joint tissue by physical forces as a single event of trauma or by repeated microtrauma due to altered mechanical loading of the joint (Brandt *et al*., 2009). Chondrocytes respond to the physical injury by stopping the production of anabolic factors and by releasing more catabolic enzymes such as MMPs, which results in further damage to the cartilage (Lane *et al*., 2000), and this further leads to the release of matrix components, which elicit inflammatory mechanisms (Jasin, 1998). Involvement of an immune response, both innate and adaptive, in OA is now widely accepted based on the following evidence:

* An inflammatory synovium/synovitis has been linked to increased cartilage damage (Ayral *et al*., 2005) and pain (Hill *et al*., 2007) in recent epidemiological studies on large number of OA patients.
* Infiltrates of immune cells including T-cells, B-cells and macrophages have been detected in synovial tissue of OA patients (Revell *et al*., 1998; Sakkas *et al*., 1998; Nakamura *et al*., 1999).
* Immunoglobulins and immune complexes against cartilage components are detected in cartilage, synovium and plasma in OA patients (Jasin, 1998).

Key role of complement activation in OA synovium has been identified (Wang *et al.,* 2011)

Here we provide a review and recent updates on the involvement of major aspects of immune system, including innate and adaptive immune responses, in the pathogenesis of OA.

Osteoarthritis (OA) is the most common type of arthritis. The occurrence of symptomatic OA is at least 12.1% in both sexes, whereas the occurrence of radiographically defined OA is much higher and rises with age (Lawrence *et al*., 1998). OA is a heterogeneous disease, and its classification leaves much to be anticipated (Altman *et al*., 1986; Altman *et al*., 1990; Altman *et al*., 1991). Primary OA, which has no outward predisposing factor, and secondary OA, in which the patient has a previous trauma or condition related to OA, are the 2 most common subsets. Primary OA is referred to as generalized OA when it affects many joints, nodal OA when it exhibits as nodes over interphalangeal joints, and erosive inflammatory OA when it exhibits as erosions in distal interphalangeal joints. Erosive inflammatory arthritis, which is categorized by flares of inflammation in joints and the occurrence of inflammation markers in peripheral blood, may represent the far end of the spectrum of generalized OA. Current treatments for OA are purely palliative, and the need for novel therapies is obvious. The etiology of primary OA is not identified. Unidentified genetic factors have been implicated in the development of OA (Holderbaum *et al*., 1999; MacGregor *et al*., 2000), and a genetic component is reinforced by studies of families and twins (Stecher *et al*., 1953). Clonal chromosome aberrations, such as the gain of chromosomes 5 and 7, were detected in the synovial membrane of certain patients with OA (Broberg *et al*., 1997). Alpha1-antitrypsin (Pattrick *et al*., 1989), 1-antichymotrypsin (Sakkas *et al*., 1990), gene polymorphisms, and HLA alleles (Pattrick *et al*., 1989; Doherty *et al*., 1990) have been associated with generalized OA, whereas type II procollagen gene polymorphisms have been associated with precocious OA with mild chondrodysplasia (Ala-Kokko *et al*., 1990).

Although the pathophysiology of OA is not quite understood, it is commonly believed that primary OA is mainly a disease of articular cartilage that may be triggered by a biomechanical alteration, i.e., abnormal forces acting on normal cartilage or normal forces acting on abnormal cartilage (Pelletier *et al*., 1997). Articular cartilage consists of chondrocytes and extracellular matrix (ECM). ECM contains water and certain macromolecules, including collagen, proteoglycans, and hyaluronic acid. Microscopic examination has revealed a loss of proteoglycans and proliferation of chondrocytes in the cartilage of patients with early OA (Hough *et al*., 2001). As the disease progresses, loss of chondrocytes and calcification occurs (Hough *et al*., 2001). The pathogenic mechanisms that lead to cartilage destruction and bone proliferation are unknown. Point mutations of ECM macromolecules in articular cartilage have been reported (Ala-Kokko *et al*., 1990). The structure of ECM molecules can also be changed by mutations in enzymes that cause post translational modification of collagen and the side chains of proteoglycan (Holderbaum *et al*., 1999). Mutations in collagen or its modifying enzymes may be the reason for subtle defects in cartilage. In that event, environmental factors, such as repetitive joint stress, may be responsible, at least in part, for the manifestation of OA. Proteolytic enzymes such as matrix metalloproteinases (MMPs) and their inhibitors seem to play an important part in cartilage matrix degradation (Mansell and Bailey, 1998). However, alterations in OA are not restricted to cartilage. In subchondral bone, there are early changes such as increased trabecular bone and stiffness (Gevers *et al*., 1989), as well as late changes such as the presence of cysts and osteophytes, which are the hallmarks of OA. Furthermore, considerable inflammation occurs in the synovial membrane. Although OA has been considered by rheumatologists, in general, to be a noninflammatory disease, accumulating evidence suggests that this is not the case. Inflammation in the synovial membrane of at least 50% of patients with OA is well documented. This inflammatory response exhibits features of a T cell immune response.

**1.2.1 Involvement of T and B cells in the pathogenesis and progression in osteoarthritis**

1. CD3+ T cells penetrate the synovial membrane of patients with OA. Several groups of investigators (Linblad and Hedfors, 1987; Haraoui *et al*., 1991; Kennedy *et al*., 1988; Myers *et al*., 1990; Smith *et al*., 1997; Haywood *et al*., 2003) have reported the occurrence of mononuclear cell (MNC) infiltrates containing T cells and macrophages in the synovial membrane of >50% of patients with OA. MNC infiltrates may be diffuse or perivascular nodular (Linblad and Hedfors, 1987; Sakkas *et al*., 1988; Sakkas *et al*., 2000). It was observed that angiocentric infiltrates composed mainly of CD3+ T cells in the synovial membrane of patients with OA in a pattern similar to that observed in RA. Transmural CD3+ T cells infiltrating the vessel wall were evident, although they were situated mainly in perivascular areas. Many vessels were compressed and obstructed, and endothelial cells were strongly positive for E-selectin, in a manner similar to that observed in RA. All of these observations in patients with OA are in addition to the findings in patients with the relatively uncommon type of erosive inflammatory disease, which clearly shows a strong inflammatory component (Moskowitz *et al*., 1992). In certain patients with OA, the MNC infiltrates resemble those observed in the synovial membrane of patients with RA (Linblad and Hedfors, 1987; Sakkas *et al*., 1988). Nodular lymphocytic aggregates were observed in 14% of patients with early OA and in 37% (Smith *et al*., 1997) to 65% (Sakkas *et al*., 1988) of patients with advanced OA at the time of joint replacement surgery. The presence of lymphoid nodular aggregates in these MNC infiltrates suggests an antigen-driven process. It has been suggested that the synovial inflammation observed in OA is a secondary phenomenon caused by fragments of cartilage or by crystals (Kennedy *et al*., 1988). This view is contradicted by the finding that lymphoid follicles are present to a greater extent in primary OA than in mechanical or traumatic OA, and detritic fragments of bone, cartilage, calcium pyrophosphate crystals, or apatite-like material do not correlate with inflammatory infiltrates (Revell *et al*., 1998; Van Linthoudt *et al*., 1997).

2. T cells infiltrating the synovial membrane of patients with OA express early, intermediate, and late activation antigens. It was previously demonstrated that in the majority of patients with advanced OA, T cells infiltrating the synovial membrane express early activation antigens (CD69), intermediate activation antigens (CD25, CD38), and late activation antigens (CD45RO, HLA class II) (Sakkas *et al*., 1988). These activation antigens were expressed on T cells and other MNCs infiltrating the synovial membrane of both patients with OA and patients with RA, although their proportions were significantly higher in patients with RA than in those with OA (Sakkas *et al*., 1988). Although it could be argued that CD45RO+ T cells may extravasate from peripheral blood, the expression of CD69, an early activation antigen, suggests that activation occurs in situ, in the synovial membrane. CD38 and the CD43, which are detected in the synovial membrane of patients with OA (Sakkas *et al*., 1988), mediate adhesion to vascular endothelium and binding to intercellular adhesion molecule 1 (ICAM-1), respectively. Leukocytes and endothelial adhesion molecules are also expressed in the synovial membrane of patients with OA, although to a lesser degree than in patients with RA (Kosh *et al*., 1991; Tak *et al*., 1995). B cells are also activated in patients with OA (Jasin,1985).

4. T cell cytokines are formed in the synovial membrane of patients with OA. Interleukin-2 (IL-2), interferon-ᵧ (IFNᵧ), and IL-10 transcripts were shown in the synovial membrane of 50% of patients with OA and in the synovial membrane of the majority of patients with RA (Sakkas *et al*., 1988). IL-4 or IL-5 transcripts were not detected by polymerase chain reaction (PCR) amplification in the synovial membrane of patients with OA, suggesting the presence of a Th1 cytokine pattern in the synovial membrane of patients with OA (Sakkas *et al*., 1988). A predominant Th1 cytokine pattern has also been detected in the synovial membrane of patients with RA (Sakkas *et al*., 1988; Simon *et al*., 1994; Dolhain *et al*., 1996). Quantitative PCR analysis using MIMIC demonstrated that IFNᵧ transcript levels in OA were similar to those in RA, when normalized for T cell equivalents (Sakkas *et al*., 1988). This means that T cells infiltrating the synovial membrane of patients with OA are as active as those infiltrating the synovial membrane of patients with RA, although they are present in lower numbers in OA (Sakkas *et al*., 1988). IFNᵧ protein was detected by immunohistochemistry in the synovial membrane of most patients with OA (Dolhain *et al*., 1996). Th1-type cytokine transcripts were also found in MNCs from the synovial fluid of patients with OA (Haynes *et al*., 2002). Both IFNᵧ protein (Kahle *et al*., 1992; Schlaak *et al*., 1996) and IL-4 protein (Schlaak *et al*., 1996) were detected in the synovial fluid of patients with OA. Because IL-12 is a major inducer of Th1 cytokines (Trinchieri, 1995), we examined whether IL-12 was produced in the synovial membrane of patients with OA and patients with RA. IL-12 was detected, at both the messenger RNA level (IL-12 p40) and the protein level (IL-12 p70) in the synovial membrane of the majority of patients with OA or RA (Sakkas, 1998). IL-12, which is produced by macrophages during phagocytosis, even of inert material (Fulton *et al*., 1996), may drive the cytokine pattern in the OA synovial membrane toward the Th1 pattern (Sakkas, 1998). In addition to IL-12, other molecules may participate in the Th1 cell response in OA, including chemokines such as IL-8 and macrophage inflammatory protein 1α (MIP-1 α). T cells producing Th1 cytokines express CCR5 on the cell surface. CCR5 is a receptor for MIP-1α, a T cell chemoattractant (Loetscher *et al*., 1998; Qin *et al*., 1998) that is up-regulated in the synovial fluid of patients with OA (Koch *et al*., 1995). Th1 cells may be driven into the synovial membrane of patients with OA by inciting antigens and/or IL-12 or chemokines. IL-10 transcripts have been observed in the synovial membrane of nearly all OA patients examined (Sakkas *et al*., 1988), often in addition to IFN and IL-2 transcripts (Sakkas *et al*., 1988). IL-10 has been classified as an anti-inflammatory Th2 cytokine in mice (Joosten *et al*.,1997). IL-10 in humans cooperates with IL-4 to inhibit the production of proinflammatory cytokines by adherent rheumatoid synovial cells (Sugiyama *et al*., 1995). However, IL-10 in humans is produced by both monocytes and Th1 cells (Winhagen *et al*., 1996). In conclusion, proinflammatory Th1 cytokines (such as IFNᵧ and IL-2) and IL-10 are expressed in the synovium of patients with OA. Peripheral blood mononuclear cells (PBMCs) from patients with OA have been shown to express levels of CCR1, CCR3, CCR5, CCR6, and CCR7 chemokines comparable with the levels expressed by PBMCs from patients with RA (Haringman *et al*., 2006). Serum levels of the activation induced T cell–derived chemokine-related cytokine lymphotactin, which is a lymphocyte chemoattractant, were similar in patients with OA and those with RA (Blascke *et al*., 2003).

5. Autoantibody responses in OA. Low numbers of B cells infiltrate the synovial membrane of patients with OA (Smith *et al*., 1992). CXCL13, a potent chemoattractor of B cells, is expressed in lymphoid aggregates in the OA synovial membrane (Shi *et al*., 2001). Single-strand conformation polymorphism analysis of immunoglobulin transcripts isolated from the synovial membrane of 6 patients with OA revealed the presence of oligoclonal B cells (Shiokawa *et al*., 2001). Highly mutated immunoglobulin VH genes were observed in OA synovial membrane (Krenn *et al*., 1999). Autoantibodies against specific target antigens were detected in patients with OA as early as 20 years ago (Jasin,1985; Mollenhauer *et al*. 1988), although they have attracted little attention. One study demonstrated that anti–cartilage intermediate layer protein, anti–YKL-39, antiosteopontin, and anti–cyclic citrullinated peptide (anti-CCP) antibodies were detected in patients with early-stage knee OA but not in those with late-stage knee OA (Du *et al*., 2004). However, according to other investigators, anti-CCP antibodies are a marker for RA, with a specificity of 98% (Schellekans *et al*., 1998). Anti–type II collagen antibodies were found in cartilage extracts from 50% and 60%, respectively, of patients with OA and patients with RA (Jasin, 1985). However, the frequency of IgG anti–type II collagen antibodies in the serum was significantly higher in patients with RA than in patients with OA (Cook *et al*., 2004; Burkhadt *et al*., 2002). Serum anti–type II collagen antibodies specific for the type II collagen epitope F4, which is no arthritogenic in mice, were associated with OA (Burkhardt *et al*., 2002). In contrast, sera with increased levels of anti–type II collagen antibodies specific for the C1(III) epitope, which is arthritogenic in mice, were prevalent in patients with RA (Burkhardt *et al*., 2002). Anti–type II collagen antibodies were also detected in sera from patients with other rheumatic conditions and from normal donors (Burkhardt *et al*., 2002). The presence of autoantibodies to arthritis related antigens during the early stage of knee OA suggests that a specific immune response may be responsible for the initial degradation of cartilage in OA (Du *et al*. 2004). Recently, a proteomic-based approach was used to identify chondrocyte autoantigens in OA and RA (Xiang *et al*., 2004). Chondrocyte proteins were separated by 2-dimensional gel electrophoresis, and sera from patients with OA or RA were used to detect antigenic polypeptides by Western blotting. These polypeptides were identified by mass fingerprinting. Sera from patients with OA recognized 19 protein spots, whereas none of these spots was recognized by sera from patients with RA. One of these antigens was identified as triosephosphate isomerase (TPI), a glycolytic enzyme that interconverts Dglyceraldehyde-3-phosphate and dihydroxyacetone phosphate (Xiang *et al*., 2004). IgG anti-TPI antibodies were found in the serum and the synovial fluid of ~25%ofthepatients with OA tested, whereas anti-TPI antibodies were found in <6% of the patients with RA or systemic lupus erythematosus (SLE) (Xiang *et al*., 2004). These results revealed an OA autoimmune profile that is different from that observed in RA (Xiang *et al*., 2004).

 6. T cells infiltrating the synovial membrane of patients with OA contain oligoclonal populations of T lymphocytes. T cells comprise large numbers of different T cell clones, which are distinguished from each other by expressing different, although highly homologous, TCRs for antigens. Each of these TCRs is a unique fingerprint of the corresponding T cell clone. The size of the T cell repertoire in peripheral blood is estimated to be in the order of 106 different β -chain TCR transcripts, each one pairing with at least 25 TCR α -chains (Artsila *et al*., 1999). These numbers of T cell clones are still very large and are sufficient to permit recognition of all conceivable antigenic epitopes. T cells are activated and proliferate either in response to specific antigens (antigen-driven proliferation) or in a nonspecific manner (antigen-independent proliferation). Nonspecific activation and proliferation could occur either in response to mitogens or chemokines or in response to super antigens and in both cases will result in a large, heterogeneous, polyclonal population of T cells comprising different T cell clones expressing unique β -chain TCR transcripts, when compared with each other. T cells activated in response to super antigens will utilize β -chain TCRs comprising a restricted number of Vβ gene segments and a unique third complementarity-determining region (CDR3), when compared with each other. In contrast, specific antigen–driven stimulation of T cells would result in proliferation and clonal expansion of only those T cell clones that recognize the specific antigen. Thus, a specific antigen–driven clonal T cell response is identified by the presence of multiple identical TCR transcripts. Because of the large number of β -chain TCR transcripts, the probability is negligible that multiple identical copies of a single β -chain TCR transcript within an independent sample of T cells will be found by chance. Therefore, the presence of multiple identical copies of a β -chain TCR transcript within an independent sample of T cells, such as those infiltrating the synovial membrane of patients with OA, must be the result of specific antigen–driven proliferation and clonal expansion of a T cell clone(s) in response to a specific antigen, resulting in the presence of substantial proportions of monoclonal or oligoclonal T cells. To determine whether multiple identical proportions of TCR transcripts are present in a particular population of T cells, β -chain and/or β -chain TCR transcripts were amplified by PCR, followed by cloning and sequencing, or by assessing the length of the CDR3 of the amplified TCR transcripts by CDR3 Spectro typing (β-chain TCR only) (Gorski *et al*., 1994). Both approaches require that separate PCR amplifications be carried out for each one of the 32 Vα and 26 Vβ families to which all known human Vα and V β segments have been classified (Arden *et al*., 1995). Different 5’-end amplification primers must be synthesized, and different PCR amplifications must be carried out for each family. Such an approach has several limitations, the most important of which are that quantitation of the results may be limited by different amplification efficiencies and that the approach is laborious. To address these limitations, we developed a PCR amplification method specifically designed for the amplification of transcripts with variable or unknown 5’ ends, such as the TCRs and immunoglobulins. This method has been designated nonpalindromic adaptor PCR(NPA-PCR) (Slachta *et al*., 2000; Olezak *et al*., 2001; Sakkas *et al* 2002; Xu *et al*., 2003; Lin *et al*., 2005; Pappas *et al*., 2005).This approach was used to study the presence of specific antigen–driven populations of T cells in several diseases (Slachta *et al*., 2000; Olezak *et al*., 2001; Sakkas *et al* 2002; Xu *et al*., 2003; Lin *et al*., 2005; Pappas *et al*., 2005), with the overall objective of identifying the antigen(s) recognized by these clonally expanded T cells. NPA-PCR has certain distinct advantages over classic PCR techniques for the amplification of transcripts with unknown or variable 5’ ends. The major advantage is that only one amplification is needed for the α -chain, with a second amplification needed for the β-chain TCR.

**1.2.2 B cells and humoral immunity in OA**

Cellular infiltrates in the inflamed OA synovium have been reported to contain activated B cells along with other cell types (Revell *et al*., 1988). A clonal analysis of B cells in OA synovium revealed their oligoclonal nature suggesting an antigen driven activation instead of non-antigenic activation (Shiokawa *et al*., 2001). Moreover, several studies found antibodies against cartilage components highlighting the activation of humoral adaptive immune response in OA. When cartilage cell surface proteins were used as substrate in an ELISA and sera from OA patients were applied, an elevated antibody titer was detected compared to controls (Mollenhauer *et al*., 1998). Similarly, autoantibodies were found in OA patients against cartilage derived proteins osteopontin (Sakata *et al*., 2001), cartilage intermediate layer protein (CILP) (Tsuruha *et al*., 2001), YKL-39, (Tsuruha *et al*., 2002), fibulin-4 (Xiang *et al*., 2004) and collagen (Charrière *et al*., 1988). Anti-CCP antibodies were detected in 7 out of 136 OA patients (Du *et a*l., 2005), while another group also detected them in OA patients but at significantly lower levels compared to RA patients (Caspi *et al*., 2006). Antibodies against native G1 domain of aggrecan core protein were found in synovial fluid of OA patients (Karopoulos *et al*., 1996). Using proteomic approach, Xiang *et al* (2004) identified triosephosphate isomerase (TPI) as an important antigen with autoantibodies present specifically in OA but not in RA (Xiang *et al*., 2004). Other studies have reported autoantibodies in animal models of OA including horses (Niebauer *et al*., 1988) and dogs (De Rooster *et al*., 2000). The role of the autoantibodies against cartilage components in development of OA has been further highlighted by studies showing their deposition (Jasin, 1985; Cooke, 1987) and cytotoxic effects on cartilage (Takagi and Jasin, 1992), which may be one of the mechanisms playing important role in cartilage degeneration in OA.

**1.3 Rheumatoid arthritis (RA)**

Recently, there has been a signiﬁcant increase in our understanding of the pathogenesis of RA; however, its aetiology remains to be fully elucidated. RA is an autoimmune disease characterized by inﬁltration of inﬂammatory cells in the synovial membrane of affected joints, leading to pannus formation. The precise induction and progression of this process remains unclear. However, the presence of T- and B-cell inﬁltrates in the inﬂamed synovial tissue is a consistent histological ﬁnding in RA (Kim and Berek, 2000). Genetic studies have demonstrated that RA is strongly correlated with the major histocompatibility complex class II antigen HLA-DR4 (Choi and Panayi, 2001). The main function of HLA-DR molecules is to present antigenic peptides to T cells. The synovial membrane contains a large number of CD4þ ‘helper’ T cells, which when activated are known to play an important role in the pathogenesis of RA. Furthermore, autoantibodies, such as RF, appear to be associated with more aggressive articular disease, a higher frequency of extra-articular manifestations and increased mortality and morbidity (Choi and Panayi, 2001).

**1.3.1 Role of T cells in the pathogenesis of RA**

 The role of T cells in the pathogenesis of RA is well established. The RA disease process is thought to be dependent on a trimolecular complex consisting of antigenic peptides, T-cell receptors and HLA-DR4. In RA, the antigen presenting cells (APCs) take up one or more unknown antigens and process them into peptides that are inserted into the groove of HLA-DR4 located on the surface of the APC. T cells with the appropriate T-cell receptors then engage with this complex (forming a trimolecular complex) to become activated. Subsequently, this causes a number of events including the production of interleukin-2 (IL-2), which leads to the clonal expansion of T cells (Kotake *et al*.,1999). After the T cells become activated, in addition to the release of cytokines (such as IL-2), a number of other changes occur to the T cells. The T cells begin to grow larger and start to express a number of surface molecules, such as CD69, tumour necrosis factor-α (TNF-α) and rANK ligand (RANKL). CD69, a cell surface signaling molecule, is involved in the activation of macrophages, TNF-α is involved in the activation of synovial ﬁbroblasts and RANKL plays a role in osteoclast activation. Following these surface changes, T cells produce the soluble mediators IL-17 and interferon-β (IFN-β) (Choi and Panayi, 2001). IL-17 has been implicated in osteoclast activation causing bone resorption in RA (Kotake *et al*., 1999). IFN-β stimulates macrophages to secrete a large number of pro-inﬂammatory cytokines. IL-1, IL-6 and TNF-α are the key cytokines thought to be responsible for stimulation of the synovial ﬁbroblasts or synoviocytes (Butler *et al*., 1995; Dayer, 2003). These key inﬂammatory cytokines induce inﬂammation and the release of matrix metalloproteinases that degrade the connective tissue and are involved in pannus formation (Choi and Panayi, 2001). The activated T cells also express osteoprotegerin ligand which, together with cytokines such as IL-1, stimulate osteoclast activation leading to bone erosion. This sequence of events leads to the chronic inﬂammation that causes damage to cartilage and bone in RA. Although there has been controversy surrounding the evidence for T-cell-stimulated cytokine release in RA synovial membrane, the early research work of Dayer and colleagues (Isler *et al*., 1993; Lacraz *et al*., 1993) and, more recently, that of McInnes *et al* (2000) can help to shed some light on this issue. They have demonstrated that activated T cells found in the synovial ﬂuid and membrane of patients with RA can directly engage with and activate the macrophages, synoviocytes and osteoclasts by cell-to-cell interactions.

**1.3.2 The role of B cells in RA**

Although the role of T cells and APCs in the pathogenesis of RA has been studied extensively, the precise role of B cells is still not well characterized. An important characteristic of RA is chronic inﬂammation of the synovial tissue in the affected joints. In contrast to normal synovial tissue, inﬁltrating lymphocytes are commonly seen in the inﬂamed synovial tissue (Kim and Berek, 2000). These inﬁltrates within the synovial membrane may be diffuse or follicular in structure. The diffuse inﬁltrate lacks a distinct structural organization, whereas the follicular inﬁltrate consists of a perivascular aggregation of T cells peripherally surrounded by B cells. One of the main cellular components of the follicular inﬁltrates are B cells, which can differentiate into plasma cells (Kim and Berek, 2000). Approximately 30% of patients with RA have synovia that show follicular inﬁltrates (Gause and Berek). B-cell development initiates in the bone marrow, where stem cells progress through various stages of differentiation to become immature B cells. Immature B cells express functional surface immunoglobulin (Ig) M whilst still in the bone marrow, before migrating (as mature B cells) to peripheral lymphoid tissues including the lymph nodes (Zhang and Bridges, 2000). Within the lymphoid follicles (follicular inﬁltrates) mature B cells can then be induced by antigens to proliferate and express IgA, IgG and IgE in addition to IgM (germinal center cells). These germinal center cells can further differentiate into plasma cells, which secrete immunoglobulins. The development of germinal centers within affected tissues is a frequent ﬁnding in organ-speciﬁc and generalized autoimmune disorders. Pro-inﬂammatory cytokines, including TNF-α and lymphotoxin- α, may play a major role in promoting the organization of germinal centers in inﬂammatory lymphoid tissues (Kim and Berek, 2000; Gause and Berek, 2001). Hence in RA there is an abundance of B cells present within the synovial membrane of affected joints and these lymphocytes can be organized into lymphoid structures. B cells can play a number of potentially critical roles in the pathogenesis of RA. They may function as APCs by processing and presenting antigenic peptides to the T cells (Choi and Panayi, 2001; Carson *et al*., 1991; Chestnut and Grey, 1986; Metlay *et al*., 1989; Takemura *et al*., 2001). The T cells then proliferate and exert pro-inﬂammatory activities. It is well known that B cells can bind antigens through their immunoglobulin receptor. The immunoglobulin receptor lies on the surface of the B cell and can bind a very low level of antigen from the environment. The antigen is degraded by the B cell into antigenic peptides. These antigenic peptides are then presented in the groove of the HLA-DR4 molecule to activate the T cells, which in turn undergo various processes, including proliferation, cytokine production and cell-to-cell interaction, which contribute to the pathogenic process in RA (Chestnut and Grey, 1986).

REFERENCES

* Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH (1998) Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 41:778–99.
* Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K (1986) *for the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association.* Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 29:1039–49.
* Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K. (1990) The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 33:1601–10.
* Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K. (1991) The American College of Rheumatology criteria for classification and reporting of osteoarthritis of the hip. Arthritis Rheum 34:505–14.
* Holderbaum D, Haggi TM, Moskowitz RW. (1999) Genetics and osteoarthritis: exposing the iceberg. Arthritis Rheum 42:397–405.
* MacGregor AJ, Antoniades L, Matson M, Andrew T, Spector TD. (2000) The genetic contribution to radiographic hip osteoarthritis in women: results of a classic twin study. Arthritis Rheum 43: 2410–6.
* Stecher RM, Hersh AH, Solomon WM, Wolpaw R. (1953) The genetics of rheumatoid arthritis: analysis of 224 families. Am J Hum Genet 5:118–38.
* Broberg K, Limon J, Palsson E, Lindstrand A, Toksvig-Larsen S, Mandahl N. (1997) Clonal chromosome aberrations are present in vivo in synovia and osteophytes from patients with osteoarthritis. Hum Genet 101:295–8.
* Pattrick M, Manhire A, Ward AM, Doherty M. (1989) HLA-A, B antigens and 1-antitrypsin phenotypes in nodal generalised osteoarthritis and erosive osteoarthritis. Ann Rheum Dis 48:470–5.
* Sakkas LI, MacFarlane DG, Bird H, Welsh KI, Panayi GS. (1990) Association of osteoarthritis with homozygosity for a 5.8 kb Taq I fragment of the 1-antichymotrypsin gene. Br J Rheumatol 29:245–8.
* Doherty M, Pattrick M, Powell R. (1990) Nodal generalised osteoarthritis is an autoimmune disease. Ann Rheum Dis 49:1017–20.
* Ala-Kokko L, Baldwin CT, Moskowitz RW, Prockop DJ. (1990) Single base mutation in the type II procollagen gene (COL2A1) as a cause of primary osteoarthritis associated with a mild chondrodysplasia. Proc Natl Acad SciUSA 87:6565–8.
* Pelletier JP, Martel-Pelletier J, Howel DS. (1997) Etiopathogenesis of osteoarthritis. In: Koopman WJ, editor. Arthritis and allied conditions. Baltimore: Williams & Wilkins; p. 1969–1984.
* Hough AJ. (2001) Pathology of osteoarthritis. In: Koopman WJ, editor. Arthritis and allied conditions. Baltimore: Williams & Wilkins; p. 2167–2194.
* Mansell JP, Bailey AJ. (1998) Abnormal cancellous bone collagen metabolism in osteoarthritis. J Clin Invest 101:1596–1603.
* Gevers G, Dequeker J, Geusens P, Nyssen-Behets C, Dhem A. (1989) Physical and histo-morphological characteristics of iliac crest bone differ according to the grade of osteoarthritis at the hand. Bone 10:173–177.
* Lindblad S, Hedfors E. (1987) Arthroscopic and immunohistologic characterization of knee joint synovitis in osteoarthritis. Arthritis Rheum 30:1081–1088.
* Haraoui B, Pelletier JP, Cloutier JM, Faure MP, Martel-Pelletier J. (1991) Synovial membrane histology and immunopathology in rheumatoid arthritis and osteoarthritis: in vivo effects of antirheumatic drugs. Arthritis Rheum 34:153–163.
* Kennedy TD, Plater-Zyberk C, Partridge TA, Woodrow DF, Maini RN. (1988) Morphometric comparison of synovium from patients with osteoarthritis and rheumatoid arthritis. J Clin Pathol 41:847–852.
* Myers SL, Brandt KD, Ehlich JW, Braunstein EM, Shelbourne KD, Heck DA. (1990) Synovial inflammation in patients with early osteoarthritis of the knee. J Rheumatol 17:1662–1669.
* Smith MD, Triantafillou S, Parker A, Youssef PP, Coleman M. (1997) Synovial membrane inflammation and cytokine production in patients with early osteoarthritis. J Rheumatol 24:365–371.
* Haywood L, McWilliams DF, Pearson CI, Gill SE, Ganesan A, Wilson D. (2003) Inflammation and angiogenesis in osteoarthritis. Arthritis Rheum 48:2173–2177.
* Sakkas LI, Scanzello C, Johanson N, Burkholder J, Mitra A, Salgame P. (1988) T cells and T-cell cytokine transcripts in the synovial membrane in patients with osteoarthritis. Clin Diagn Lab Immunol 5:430–437.
* Sakkas LI, Scanzello CR, Katsetos CD, Johanson NA, Platsoucas CD. (2000) Angiocentric inflammation in the synovial membrane (SM) in osteoarthritis (OA) Rheumatology 39 Suppl 177:218.
* Moskowitz RW, Howell DS, Goldberg VM, Mankin HJ, (1992) Osteoarthritis: diagnosis and medical/surgical management. Philadelphia: WB Saunders
* Revell PA, Mayston V, Lalor P, Mapp P. (1988) The synovial membrane in osteoarthritis: a histological study including characterization of the cellular infiltrate present in inflammatory osteoarthritis using monoclonal antibodies. Ann Rheum Dis 47:300–307.
* Van Linthoudt D, Beutler A, Clayburne G, Sieck M, Fernandes L, Schumacher HR Jr. (1997) Morphometric studies on synovium in advanced osteoarthritis: is there an association between apatite like material and collagen deposits. Clin Exp Rheumatol 15:493–497.
* Jasin HE. (1985) Autoantibody specificities of immune complexes sequestered in articular cartilage in patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum 28:241–248.
* Cook AD, Gray R, Ramshaw J, Mackay IR, Rowley MJ. (2004) Antibodies against the CB10 fragment of type II collagen in rheumatoid arthritis. Arthritis Res Ther 6:477–483.
* Mollenhauer J, von der Mark K, Burmester G, Gluckert K, Lutjen-Drecoll E, Brune K. (1988) Serum antibodies against chondrocyte cell surface proteins in osteoarthritis and rheumatoid arthritis. J Rheumatol 15:1811–1817.
* Burkhardt H, Koller T, Engstrom A, Nandakumar KS, Turnay J, Kraetsch HG. (2002) Epitope-specific recognition of type II collagen by rheumatoid arthritis antibodies is shared with recognition by antibodies that are arthritogenic in collagen-induced arthritis in the mouse. Arthritis Rheum 46:2339–2348.
* Xiang Y, Sekine T, Nakamura H, Imajoh-Ohmi S, Fukuda H, Nishioka K. (2004) Proteomic surveillance of autoimmunity in osteoarthritis: identification of triosephosphate isomerase as an autoantigen in patients with osteoarthritis. Arthritis Rheum 50:1511–1521.
* Du H, Masuko-Hongo K, Nakamura H, Xiang Y, Bao CD, Wang XD. (2004) The prevalence of autoantibodies against cartilage intermediate layer protein, YKL-39, osteopontin, and cyclic citrullinatedpeptideinpatientswithearly-stagekneeosteoarthritis: evidence of a variety of autoimmune processes. Rheumatol Int 26:35–41.
* Schellekens GA, de Jong BA, van den Hoogen FH, van de Putte LB, van Venrooij WJ. (1998) Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. J Clin Invest 101:273–281.
* Simon AK, Seipelt E, Sieper J. (1994) Divergent T-cell cytokine patterns in inflammatory arthritis. Proc Natl Acad SciUSA 91: 8562–6.
* Dolhain RJ, van der Heiden AN, ter Haar NT, Breedveld FC, Miltenburg AM. (1996) Shift toward T lymphocytes with a T helper 1 cytokine–secretion profile in the joints of patients with rheumatoid arthritis. Arthritis Rheum 39:1961–9.
* Klimiuk PA, Goronzy JJ, Bjornsson J, Beckenbaugh RD, Weyand CM. (1997) Tissue cytokine patterns distinguish variants of rheumatoid synovitis. Am J Pathol 151:1311–9.
* Dolhain RJ, ter Haar NT, Hoefakker S, Tak PP, de Ley M, Claassen E. (1996) Increased expression of interferon (IFN)together with IFN receptor in the rheumatoid synovial membrane compared with synovium of patients with osteoarthritis. Br J Rheumatol 34:24–32.
* Haynes MK, Hume EL, Smith JB. (2002) Phenotypic characterization of inflammatory cells from osteoarthritic synovium and synovial fluids. Clin Immunol 105:315–25.
* Kahle P, Saal JG, Schaudt K, Zacher J, Fritz P, Pawelec G. (1992) Determination of cytokines in synovial fluids: correlation with diagnosis and histomorphological characteristics of synovial tissue. Ann Rheum Dis 51:731–4.
* Schlaak JF, Pfers I, Meyer Zum Buschenfelde KH. (1996) Different cytokine profiles in the synovial fluid of patients with osteoarthritis, rheumatoid arthritis and seronegative spondylarthropathies. Clin Exp Rheumatol 14:155–62.
* Sakkas LI, Johanson NA, Scanzello CR, Platsoucas CD. (1998) Interleukin-12 is expressed by infiltrating macrophages and synovial lining cells in rheumatoid arthritis and osteoarthritis. Cell Immunol 188:105–10.
* Fulton S, Johnsen JM, Wolf SF, Sieburth DS, Boom WH. (1996) Interleukin-12 production by human monocytes infected with Mycobacterium tuberculosis: role of phagocytosis. Infect Immun 64:2523–31.
* Loetscher P, Uguccioni M, Bordoli L, Baggiolini M, Moser B, Chizzolini C. (1998) CCR5 is characteristic of Th1 lymphocytes. Nature 391:344–5.
* Qin S, Rottman JB, Myers P, Kassam N, Weinblatt M, Loetscher M. (1998) The chemokine receptors CXCR3 and CCR5 mark subsets of T cells associated with certain inflammatory reactions. J Clin Invest 101:746–54.
* Koch AE, Kunkel SL, Shah MR, Fu R, Mazarakis DD, Haines GK. (1995) Macrophage inflammatory protein-1β : a C-C chemokine in osteoarthritis. Clin Immunol Immunopathol 77: 307–14.
* Haringman JJ, Smeets TJ, Reinders-Blankert P, Tak PP. (2006) Chemokine and chemokine receptor expression in paired peripheral blood mononuclear cells and synovial tissue of patients with rheumatoid arthritis, osteoarthritis, and reactive arthritis. Ann Rheum Dis 65:294–300.
* Blaschke S, Middel P, Dorner BG, Blaschke V, Hummel KM, Kroczek RA. (2003) Expression of activation-induced, T cell–derived, and chemokine-related cytokine/lymphotactin and its functional role in rheumatoid arthritis. Arthritis Rheum 48:1858–72.
* Kim H-J, Berek C. (2000) Review: B cells in rheumatoid arthritis. Arthritis Res 2:126–31.
* Choy EH, Panayi GS. (2001) Cytokine pathways and joint inﬂammation in rheumatoid arthritis. N Engl J Med 344:907–16.
* Kotake S, Udagawa N, Takahashi N. (1999) IL-17 in synovial ﬂuids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. J Clin Invest 103: 1345–52.
* Butler DM, Maini RN Feldmann M, Brennan FM. (1995) Modulation of proinﬂammatory cytokine release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti TNF-alpha antibody with the interleukin-1 receptor antagonist. Eur Cytokine Netw 6:225–30.
* Dayer J-M. (2003) The pivotal role of interleukin-1 in the clinical manifestations of rheumatoid arthritis. Rheumatology *42*(Suppl 2): ii3–ii10.
* Isler P, Vey E, Zhang JH, Welgus HG, Dayer JM. (1993) Cell surface glycoproteins expressed on activated human T cells induce production of interleukin-1 beta by monocytic cells: a possible role of CD69. Eur Cytokine Netw 4:15–23.
* Lacraz S, Isler P, Vey E. (1994) Direct contact between T lymphocytes and monocytes is a major pathway for induction of metalloproteinase expression. J Biol Chem 269:22027–33
* McInnes IB, Leung BP, Liew FY. (2000) Cell–cell interactions in synovitis. Interactions between T lymphocytes and synovial cells. Arthritis Res 2:374–8.
* Gause A, Berek C. (2001) Role of B cells in the pathogenesis of rheumatoid arthritis: potential implications for treatment. Bio Drugs 15:73–9.
* Zhang Z, Bridges SL Jr. (2001) Pathogenesis of rheumatoid arthritis. Role of B lymphocytes. Rheum Dis Clin North Am 27:335–53.
* Carson DA, Chen PP, Kipps TJ. (1991) New roles for rheumatoid factor. J Clin Invest 87:379–83.
* Chesnut RW, Grey HM. (1986) Antigen presentation by B cells and its signiﬁcance in T–B interactions. Adv Immunol 39:51–94.
* Metlay JP, Pure´ E, Steinman RM. (1989) Control of the immune response at the level of antigen-presenting cells: a comparison of the function of dendritic cells and B lymphocytes. Adv Immunol 47:45–116.
* Takemura S, Klimiuk PA, Braun A. (2001) T cell activation in rheumatoid synovium is B cell dependent. J Immunol 167:4710–18.
* Beronius M, Bergman B, Anderson R. (2001) Vertebral osteomyelitis in Goteborg, Sweden: a retrospective study of patients during 1990–95. Scand J Infect Dis. 33:527–532.
* Dahl L B, Hoyland A L, Dramsdahl H, Kaaresen P I. (1998) Acute osteomyelitis in children: a population-based retrospective study 1965 to 1994. Scand J Infect Dis. 30:573–577.
* Trobs R, Moritz R, Buhligen U. (1999) Changing pattern of osteomyelitis in infants and children. Pediatr Surg Int. 15:363–372.
* Burnett, M.W.; J.W. Bass; B.A. Cook (1998). "Etiology of osteomyelitis complicating sickle cell disease". Pediatrics. 101 (2): 296–97. doi​: ​10.1542/peds.101.2.296​. PMID 9445507.
* Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson; & Mitchell, Richard N. (2007). Robbins Basic Pathology (8th ed.). Saunders Elsevier. pp. 810–11 ISBN 978-1-4160-2973-1
* Luqmani, Raashid; Robb, James; Daniel, Porter; Benjamin, Joseph (2013). Orthopaedics, Trauma and Rheumatology (second ed.). Mosby. p. 96. ISBN 978-0723436805.
* Ellington. (1999) Microbial Pathogenesis.
* Ellington (2003) Journal of Bone and Joint Surgery.
* Ellington. (2006) Journal of Orthopedic Research.
* King MD, Randall W, Johnson D (2006). "Osteomyelitis".
* Creamer P, Hochberg MC. (1997) Osteoarthritis. Lancet. 350:503–508.
* Brandt KD, Dieppe P, Radin E. (2009) Etiopathogenesis of osteoarthritis. Med Clin North Am. 93:1–24.
* Lane Smith R, Trindade MC, Ikenoue T. (2000) Effects of shear stress on articular chondrocyte metabolism. Biorheology. 37:95–107.
* Jasin HE. (1988) Immune mediated cartilage destruction. Scand J Rheumatol Suppl. 76:111–116.
* Ayral X, Pickering EH, Woodworth TG. (2005) Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis - results of a 1-year longitudinal arthroscopic study in 422 patients. Osteoarthritis Cartilage.13:361–367.
* Hill CL, Hunter DJ, Niu J. (2007) Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. Ann Rheum Dis. 66:1599–1603.
* Revell PA, Mayston V, Lalor P, Mapp P. (1988) The synovial membrane in osteoarthritis: a histological study including the characterization of the cellular infiltrate present in inflammatory osteoarthritis using monoclonal antibodies. Ann Rheum Dis. 47:300–307.
* Sakkas LI, Scanzello C, Johanson N. (1998) T cells and T-cell cytokine transcripts in the synovial membrane in patients with osteoarthritis. Clin Diagn Lab Immunol. 5:430–437.
* Nakamura H, Yoshino S, Kato T. (1999) T-cell mediated inflammatory pathway in osteoarthritis. Osteoarthritis Cartilage. 7:401–402.
* Wang Q, Rozelle AL, Lepus CM. (2011) Identification of a central role for complement in osteoarthritis. Nat Med. 17:1674–1679.
* Revell PA, Mayston V, Lalor P, Mapp P. (1988) The synovial membrane in osteoarthritis: a histological study including the characterization of the cellular infiltrate present in inflammatory osteoarthritis using monoclonal antibodies. Ann Rheum Dis. 47:300–307.
* Tsuruha J, Masuko-Hongo K, Kato T. (2001) Implication of cartilage intermediate layer protein in cartilage destruction in subsets of patients with osteoarthritis and rheumatoid arthritis. Arthritis Rheum. 44:838–845
* Tsuruha J, Masuko-Hongo K, Kato T. (2002) Autoimmunity against YKL-39, a human cartilage derived protein, in patients with osteoarthritis. J Rheumatol. 29:1459–1466.
* Xiang Y, Sekine T, Nakamura H. (2004) Proteomic surveillance of autoimmunity in osteoarthritis: identification of triosephosphate isomerase as an autoantigen in patients with osteoarthritis. Arthritis Rheum. 50:1511–1521.
* Charrière G, Hartmann DJ, Vignon E. (1988) Antibodies to types I, II, IX, and XI collagen in the serum of patients with rheumatic diseases. Arthritis Rheum. 31:325–332.
* Du H, Masuko-Hongo K, Nakamura H. (2005) The prevalence of autoantibodies against cartilage intermediate layer protein, YKL-39, osteopontin, and cyclic citrullinated peptide in patients with early-stage knee osteoarthritis: evidence of a variety of autoimmune processes. Rheumatol Int. 26:35–41.
* Caspi D, Anouk M, Golan I. (2006) Synovial fluid levels of anti-cyclic citrullinated peptide antibodies and IgA rheumatoid factor in rheumatoid arthritis, psoriatic arthritis, and osteoarthritis. Arthritis Rheum. 55:53–56.
* Karopoulos C, Rowley MJ, Ilic MZ, Handley CJ. (1996) Presence of antibodies to native G1 domain of aggrecan core protein in synovial fluids from patients with various joint diseases. Arthritis Rheum. 39:1990–1997.
* Niebauer GW, Wolf B, Yarmush M, Richardson DW. (1988) Evaluation of immune complexes and collagen type-specific antibodies in sera and synovial fluids of horses with secondary osteoarthritis. Am J Vet Res. 49:1223–1227.
* De Rooster H, Cox E, van Bree H. (2000) Prevalence and relevance of antibodies to type-I and -II collagen in synovial fluid of dogs with cranial cruciate ligament damage. Am J Vet Res. 61:1456–1461.
* Jasin HE. (1985) Autoantibody specificities of immune complexes sequestered in articular cartilage of patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum. 28:241–248.
* Cooke TD. (1987) Significance of immune complex deposits in osteoarthritic cartilage. J Rheumatol. 14:77–79.
* Takagi T, Jasin HE. (1992) Interactions between anticollagen antibodies and chondrocytes. Arthritis Rheum. 35:224–230
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