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**TOPIC: DISCUSS THE INVOLVEMENT OF T- AND B-LYMPHOCYTES IN THE PATHOGENESIS AND PROGRESSION OF OSTEOMYELITIS AND OSTEOARTHRITIS.**

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**The role of T cells/lymphocytes in the pathogenesis and progression of osteoarthritis (OA).**

**Introduction**

Osteoarthritis (OA) is a type of joint disease that results from breakdown of joint cartilage and underlying bone (Arden *et al.,* 2015). It is the most common type of arthritis. The prevalence of symptomatic OA is at least 12.1% in both sexes, whereas the prevalence of radiographically defined OA is much higher and increases with age (Lawrence *et al.,* 1998). Osteoarthritis is a heterogeneous disease, and its classification leaves much to be desired (Altman *et al.,* 1986). Primary OA, which has no apparent predisposing factor, and secondary OA, in which the patient has a prior trauma or condition related to OA, are the two most common subsets. Several lines that show that T cells may play an important role in the pathogenesis and progression of OA (Sakkas *et al.,* 2002), are as follows:

**1.CD3+ T cells infiltrate the synovial membrane of patients with OA.**

There is a presence of mononuclear cell (MNC) infiltrates consisting of T cells and macrophages in the synovial membrane of less than 50% of patients with osteoarthritis. Mononuclear cell infiltrates may be diffuse or perivascular nodular (Lindblad *et al.,*1987; Sakkas *et al.,* 1998; Johanson *et al.,* 2000), and it has been observed that angiocentric infiltrates is composed primarily of CD3+ T cells in the synovial membrane of patients with OA, in a pattern similar to that observed in rheumatoid arthritis (RA) (Sakkas *et al.,* 2000). In certain patients with OA, the MNC infiltrates resemble those observed in the synovial membrane of patients with RA (Lindblad *et al.,* 1987; Sakkas *et al.,* 1998). Nodular lymphocytic aggregates were observed in 14% of patients with early OA and in 37% to 65% 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 dendritic fragments of bone, cartilage, calcium pyrophosphate crystals, or apatite‐like material do not correlate with inflammatory infiltrates (Revell *et al.,* 1988; Beutler *et al.,* 1997).

**2. T cells infiltrating the synovial membrane of patients with OA express early, intermediate, and late activation antigens.**

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.,* 1998). These activation antigens were expressed on T cells and other mononuclear cells infiltrating the synovial membrane of both patients with OA and patients with rheumatoid arthritis (RA), although their proportions were significantly higher in patients with RA than in those with OA (Sakkas *et al.,* 1998). 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.,* 1998), 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 osteoarthritis, although to a lesser degree than in patients with rheumatoid arthritis (Koch *et al.,* 1991; Tak *et al.,* 1995).

**3. Human Leukocyte Antigen (HLA) association of OA.**

Several studies have demonstrated associations of osteoarthritis with HLA class I and HLA class II alleles. Studies on generalized OA revealed an association with HLA–B8 (Pattrick *et al.,* 1989; Doherty *et al.,* 1990). This association may not be primary, because HLA–B8 is in linkage disequilibrium with DR3. Another study in Japanese patients with generalized OA revealed an association with HLA–Cw4 (Wakitani *et al.,* 2001). This HLA class II association of OA further supports the concept that OA, at least in certain patients, may be a trimolecular‐complex (T cell receptor [TCR]/antigen/HLA) disease.

Interestingly, the normally HLA–DR–negative chondrocytes become positive in osteoarthritis (Burmester *et al.,* 1983; Lance *et al.,* 1993; Sakata *et al.,* 2003), suggesting that they may function as antigen‐presenting cells (APCs). Physical interaction between chondrocytes and T cells is conceivable, because cartilage fragments, which are mechanically removed from the cartilage surface, are frequently found in the synovial membrane of patients with OA (Revell *et al.,* 1988). Proliferative responses in vitro of peripheral blood T cells from patients with OA to autologous chondrocytes were significantly higher compared with those of T cells from normal control subjects (Sakata *et al.,* 2003). T cells derived from the peripheral blood or synovial fluid of patients with OA responded to membrane preparations of autologous chondrocytes and fibroblasts by proliferation (Alsalameh *et al.,* 1990). These T cell responses are monocyte dependent, suggesting an antigen‐specific immune response (Alsalameh *et al.,* 1990).

**4. T cell cytokines are produced in the synovial membrane of patients with OA.**

Interleukin‐2 (IL‐2), interferon‐γ (IFNγ), and IL‐10 transcripts in the synovial membrane of 50% of patients with OA and in the synovial membrane of the majority of patients with RA is observed (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). 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.

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 (Blaschke *et al.,* 2003).

**5. Autoantibody responses in OA.**

Autoantibodies against specific target antigens were detected in patients with osteoarthritis as early as twenty years ago (Jasin, 1985; LÜTJEN *et al.,* 1988), although they have attracted little attention. These autoantibodies are summarized in the table below 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.,* 2005). However, according to other investigators, anti‐CCP antibodies are a marker for RA, with a specificity of 98% (Schellekens *et al.,* 1998).

**Table 1. Autoantibodies in OA**

|  |  |  |
| --- | --- | --- |
| Target antigen | Frequency, % | References |
| Type II collagen | 50 | (Cook *et al.,* 2004) |
| Triosephosphate isomerase | 24.7 | (Xiang *et al.,* 2004) |
| Cartilage intermediate layer protein | 10.5-18.4 | (Du *et al.,* 2005) |
| LDL receptor–related protein 2 | 15 | (Ooka *et al.,* 2003) |
| Osteopontin | 8.1-9.5 | (Du *et al.,* 2005) |
| YKL‐39 | 6.6-9.5 | (Tsuruha *et al.,* 2002) |
| Calpastatin | 8.3 | (Iwaki *et al.,* 2004) |

**6. T cells infiltrating the synovial membrane of patients with OA contain oligoclonal populations of T lymphocytes.**

Table 2. Analysis of α/β TCR in the synovial membrane or synovial fluid of patients with OA

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| --- | --- |
| α/β TCR in the synovium of patients with OA | References |
| 1. Substantial proportions of identical β‐chain TCR transcripts were found in the synovial membrane of four of five patients with OA, after NPA‐PCR and/or Vβ‐specific PCR amplification, cloning, and sequencing. | (Scanzello *et al.,* 1999) |
| 2. Restricted usage of Vα and Vβ TCR gene segments was detected after Vα‐ and Vβ‐specific PCR amplification. | (Williams *et al.,* 1992) |
| 3. Few predominant Vα and Vβ gene segments were found in the synovial fluid from a patient with OA after PCR amplification. | (Maruyama *et al.,* 1993) |
| 4. β‐chain TCR clones, expressed at least in duplicate, and sharing common CDR3 motifs were found in the synovial membrane of patients with OA by the single‐strand confirmation polymorphism method. | (Nakamura *et al.,* 1999) |

**7. Putative OA antigens.**

T cells from the peripheral blood and synovial fluid of patients with OA exhibited strong proliferative responses to preparations of autologous chondrocyte membranes and autologous fibroblast membranes but not to epithelial cell membranes (Alsalameh *et al.,* 1990). Studies at the clonal level revealed high precursor frequencies in T cells responding to chondrocyte membranes in the peripheral blood of patients with OA. These T cell responses were strongly monocyte dependent and exhibited the characteristics of a specific antigen–driven process (Alsalameh *et al.,* 1990). Proliferative responses of peripheral blood T cells from patients with OA to irradiated autologous chondrocytes were substantially higher than those of control T cells from normal donors (Sakata *et al.,* 2003).

**8. Decreased expression of the CD3 ζ‐chain in T cells infiltrating the synovial membrane of patients with OA.**

The CD3 ζ‐chain is one of the CD3 proteins and is part of the T cell signal transduction cascade that is initiated by engagement of the TCR by appropriate antigenic epitopes and culminates in T cell activation and proliferation. Therefore, the expression of CD3ζ transcripts and protein is significantly decreased in T cells infiltrating the synovial membrane of patients with OA (Sakkas *et al.,* 2004), in a manner similar to that observed in T cells in several conditions involving chronic antigenic stimulation of T cells, including RA (Matsuda *et al.,* 1998), human immunodeficiency virus infection, leprosy, and several types of tumors (Sakkas *et al.,* 2004). Decreased expression of the CD3 ζ‐chain is associated with T cell hyporesponsiveness and energy and defective signal transduction (Sakkas *et al.,* 2004). These results suggest that chronic T cell stimulation is taking place in the synovial membrane of patients with OA, resulting in decreased expression of CD3ζ transcripts and protein in these T cells. These results support the concept of T cell involvement in OA.

In Summary;

1. T cells and monocyte/macrophages infiltrate the synovial membrane of a substantial proportion of patients with osteoarthritis.

2. Mononuclear cells infiltrating the synovial membrane of these patients express early, intermediate, and late activation antigens.

3. T cells in the synovial membrane of patients with advanced osteoarthritis often form perivascular nodules.

4. T cells infiltrating the synovial membrane of patients with osteoarthritis express Th1 cytokine transcripts and proteins.

5. Monoclonal/oligoclonal populations of T cells are present in the synovial membrane of patients with osteoarthritis, suggesting that these cells have undergone specific antigen–driven proliferation and clonal expansion, in response to an unidentified antigen or antigens.

6. T cells exhibit reduced levels of CD3 ζ‐chain transcript and protein, as in other antigen‐driven T cell responses with chronic stimulation.

7. T cells, through direct cell–cell contact or soluble mediators, can activate macrophages to degrade cartilage.

8. T cell–derived cytokines and chemokines are found in the synovial membrane of patients with osteoarthritis, and they can directly degrade cartilage.

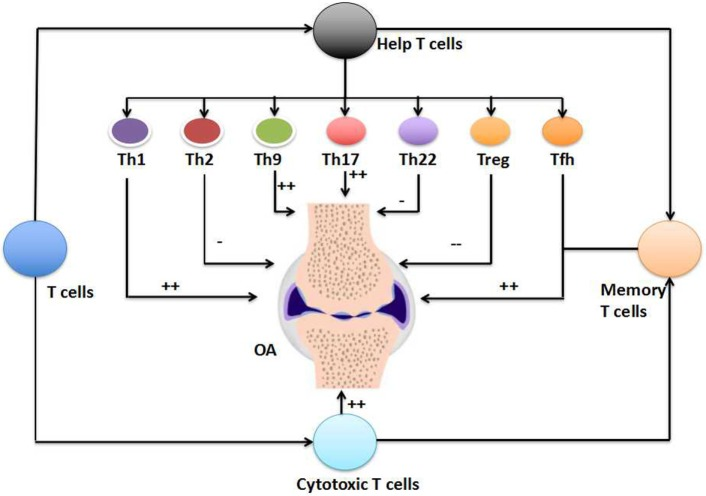


Figure 1: The involvement of T cells in the pathogenesis of osteoarthritis (OA). T cells, including the T helper (Th) cells, cytotoxic T cells, and T memory (Tm) cells, have critical importance in the pathogenesis of OA (++). The involvement of unconventional T cells in the pathogenesis of OA is not 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 (−−) (Wei *et al.,* 2017).

**The role of B cells/lymphocytes in the pathogenesis and progression of** **osteoarthritis (OA)**

Osteoarthritis is understood to be induced by mechanical stress in the form of cartilage destruction, with minimal involvement of immune responses. Thus, osteoarthritis was regarded as a non-inflammatory disease, in contrast with rheumatoid arthritis (RA), an inflammatory disease (Li *et al.,* 2016). 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 (Sakkas and Platsoucas, 2007). 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 (Fonseca *et al.,* 2002). 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. There is a reflection 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. The synovial membranes in regions rimming the cartilage of OA patients, which contain T cells bordered by B lymphocytes and plasma cells (Lindblad and Hedfors, 1987), 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 (Lindblad and Hedfors, 1987). 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 (Saito *et al.,* 2002). These findings suggested that macrophages may be associated with the pathogenesis of knee OA. Of twenty osteoarthritic synovial membranes, five showed lymphoid follicles containing T cells, B cells, and macrophages, and ten (including the latter five) displayed a diffuse cellular infiltrate containing T and B cells, macrophages, and granulocytes (Revell *et al.,* 1988). These results suggest that B cells and granulocytes may also be involved in the pathogenesis of knee OA. Low numbers of B cells infiltrate the synovial membrane of patients with osteoarthritis (Smith *et al.,* 1992). CXCL13, a potent chemo attractor 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 six patients with osteoarthritis revealed the presence of oligoclonal B cells (Shiokawa *et al.,* 2001). B cells are also activated in patients with osteoarthritis (Jasin, 1985).

**The involvement of T and B lymphocytes in the pathogenesis and progression of osteomyelitis**

Osteomyelitis (OM) is an infection of bone. Symptoms may include pain in a specific bone with overlying redness, fever, and weakness. T lymphocytes originate from precursor stem cells in fetal liver and bone marrow and differentiate into mature cell types after migration to the thymus (Yang *et al.,* 2010). They may be categorized based on their distinct function into cytotoxic T lymphocytes (expressing the surface protein cluster of differentiation (CD) 8 and responsible mainly for immune defense against intracellular pathogens and for tumor surveillance) and helper T lymphocytes (expressing the surface protein CD4) (Abbas *et al.,* 1996).

B lymphocytes develop from hematopoietic stem cells. Maturation of B cells takes place in bone marrow, whereas their activation occurs in the secondary lymphoid organs such as lymph nodes and the spleen (Kondo, 2010). B cells represent mainly the humoral immunity. However, their role as a cell itself is equally relevant. They not only participate in proinflammatory reactions but also play a role in regulation of immune responses. Recent studies identified regulatory B (Breg) cells as specific subsets that have an ability of immune response suppression (Rosser and Mauri, 2015), and they contribute to maintenance of peripheral tolerance and inhibition of immune reaction to specific self-antigens, mainly by producing of interleukin-10 (IL-10) but also by transforming growth factor (TGF-β), Fas ligand, and expressing of TNF-related apoptosis-inducing ligand (TRAIL) (Kristensen *et al.,* 2015).

Osteomyelitis may be caused from hematogenous spread, direct inoculation of microorganisms into bone, or from a contiguous focus of infection. 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, they 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, and 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. Because of the particulars of their blood supply, the tibia, femur, humerus, vertebra, maxilla, and the mandibular bodies are especially susceptible to osteomyelitis (King *et al.,* 2006).

Acute osteomyelitis presents as a suppurative infection accompanied by edema, vascular congestion, and small vessel thrombosis. In early acute disease, the vascular supply to the bone is decreased by infection extending into the surrounding soft tissue. Large areas of dead bone (sequestra) may be formed when the medullary and periosteal blood supplies are compromised (Emslie *et al.,* 1983). Acute osteomyelitis can be arrested before dead bone develops if treated promptly and aggressively with antibiotics and surgery. In an established infection, fibrous tissue and chronic inflammatory cells form around the granulation tissue and dead bone. After the infection is contained, there is a decrease in the vascular supply to it, inhibiting an effective inflammatory response. Chronic osteomyelitis is the result of the coexistence of infected, nonviable tissues and an ineffective host response (Ciampolini and Harding, 2000).

Pathologic features of chronic osteomyelitis are the presence of necrotic bone, the formation of new bone, and the exudation of polymorphonuclear leukocytes joined by large numbers of lymphocytes, histiocytes, and, occasionally, plasma cells. New bone forms from the surviving fragments of periosteum and endosteum in the region of the infection. An encasing sheath of live bone, an involucrum, surrounds the dead bone under the periosteum. The involucrum is irregular and is often perforated by openings through which purulence may enter into the surrounding soft tissues and eventually drain to the skin surfaces, forming a chronic sinus. The involucrum may gradually increase in density and thickness to form part or all of a new diaphysis. New bone increases in amount and density for weeks or months, according to the size of the bone and extent and duration of infection. Endosteal new bone may proliferate and obstruct the medullary canal. After host defense or operative removal of the sequestrum, the remaining cavity may fill with new bone, especially in children. However, in adults, the cavity may persist or the space may be filled with fibrous tissue, which may connect with the skin surface via a sinus tract (Ciampolini and Harding, 2000).

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