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

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**16/MHS01/168**

**INTRODUCTION**

**Osteomyelitis**

Osteomyelitis is an infection of bone (NORD, 2017) Symptoms may include pain in a specific bone with overlying redness, fever, and weakness (NORD, 2017). The long bones of the arms and legs are most commonly involved in children, while the feet, spine, and hips are most commonly involved in adults (GARD, 2016).

The cause is usually a bacterial infection, but rarely can be a fungal infection (NORD, 2017; GARD, 2016) It may occur by spread from the blood or from surrounding tissue (Schmitt, 2017). Risks for developing osteomyelitis include diabetes, intravenous drug use, prior removal of the spleen, and trauma to the area (NORD, 2017). Diagnosis is typically suspected based on symptoms (GARD, 2016). This is then supported by blood tests, medical imaging, or bone biopsy (GARD, 2016).

**Osteoarthritis**

Osteoarthritis is a type of joint disease that results from breakdown of joint cartilage and underlying bone (Arden *et al*.,2015). The most common symptoms are joint pain and stiffness (NIAMS, 2015). Usually the symptoms progress slowly over years (NIAMS, 2015). Initially they may only occur after exercise, but can become constant over time (NIAMS, 2015). Other symptoms may include joint swelling, decreased range of motion, and, when the back is affected, weakness or numbness of the arms and legs (NIAMS, 2015). The most commonly involved joints are the two near the ends of the fingers and the joint at the base of the thumbs; the knee and hip joints; and the joints of the neck and lower back (NIAMS, 2015). Joints on one side of the body are often more affected than those on the other (NIAMS, 2015). The symptoms can interfere with work and normal daily activities (NIAMS, 2015). Unlike some other types of arthritis, only the joints, not internal organs, are affected (NIAMS, 2015).

**Function of T and B lymphocyte**

The T and B lymphocytes (T and B Cells) are involved in the acquired or antigen-specific immune response given that they are the only cells in the organism able to recognize and respond specifically to each antigenic epitope. The B Cells have the ability to transform into plasmocytes and are responsible for producing antibodies (Abs). Thus, humoral immunity depends on the B Cells while cell immunity depends on the T Cells. In the present chapter, the processes of ontogeny are summarized for each type of lymphocyte together with their main characteristics, the different subpopulations described to date, the signaling mechanisms employed for their activation, and their main functions based on the immunological profile that they present.

**Involvement of T- and B- lymphocytes in the pathogenesis and progression osteoarthritis**

**Involvement T cells in OA**

Mononuclear cell infiltrates in synovial tissues have been reported in OA (Smith *et al.*, 1997 ; Lindblad and Hedfors, 1987 ; Sakkas *et al.,* 1988 ; kennedy *et al.,* 1988; Haraoui *et al.,* 1991) and have been shown to contain primarily CD3+ T cells (Ishii *et al.,*2002). Both CD4+ and CD8+ cells were found in OA synovium at similar levels as in RA synovium. The Th1 subset of T cells were found to be about 5 times more than Th2 cells (Ishii *et al.,*2002) and higher levels of Th1 cytokines, IL-2 and IFNγ, were detected in most of OA patients (Sakkas *et al.,* 1988). T-cells in lymphocytic aggregates in OA synovium were shown to bear early (CD69), intermediate (CD25 and CD38) and late (CD45RO) activation markers. These observations suggest the presence of an active cell-mediated immune response in majority of OA patients. Analysis of α/β T cell receptor diversity revealed the presence of oligoclonal populations of T cells in OA patients (Nakamura *et al*., 1999 ; Zwillich *et al.,* 1994 ; Scanzello *et al.,* 1999) . This suggested that those cells were undergoing clonal expansion in response to specific antigens within the synovium. Although there are no conclusive data on the antigens, which drive the immune response in OA, several candidate antigens have been proposed. T cells derived from peripheral blood and synovial fluid of OA patients showed a strong response to autologous chondrocyte and fibroblast membrane preparations (Alsalameh *et al.,* 1990). In another study OA chondrocytes were shown to stimulate autologous T cell response in vitro (Sakata *et al.,* 2003). Cellular immunity to type III collagen and proteoglycan was detected after partial meniscectomy in rabbits (Champion and Poole, 1982). Higher cellular immunity was observed in OA patients compared to normal subjects when their peripheral blood lymphocytes were stimulated with human cartilage link protein and G1 globular domain of proteoglycan ( Guerassimov *et al*., 1999). More specifically, peptides representing amino acid regions 16–31 and 263–280 located in G1 domain of proteoglycan were more frequently recognized by PBMCs isolated from OA patients compared to healthy controls (De Jong *et al*., 2010). These studies suggest a role for cartilage components as autoantigens responsible for oligoclonal T cell response observed in OA patients. The role of CD4+ T cells in OA was highlighted by a recent study in anterior cruciate ligament-transection (ACLT)-induced OA mice where these cells were found to be involved in increased production of MIP-1γ followed by increased infiltration of macrophages in synovium and increased expression of MMP-9 [101]. In another study, when chondrocytes from OA patients were co-culture with autologous T cells, they produced higher amounts of RANTES and MMP-1, MMP-3 and MMP-13 (Nakamura *et al*., 1999).

**Involvement of B cells and 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 ali., 1988*). 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*., 2001), 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 al.,*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 identified triosephosphate isomerase (TPI) as an important antigen with autoantibodies present specifically in OA but not in RA [127]. 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

**PATHOGENESIS OF OSTEOMYELITIS**

Basic methods how infection gets into the bones;

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 (Burnet *et al*., 1998).

**Involvement of T- and B- lymphocytes in the pathogenesis and progression osteomyelitis**

After further research, articles relating to the involvement of T- and B- lymphocytes in the pathogenesis of osteomyelitis haven’t been made available or been found, but with the knowledge of the disease and mechanism of action of T and B lymphocyte, when the inflammatory process begins;

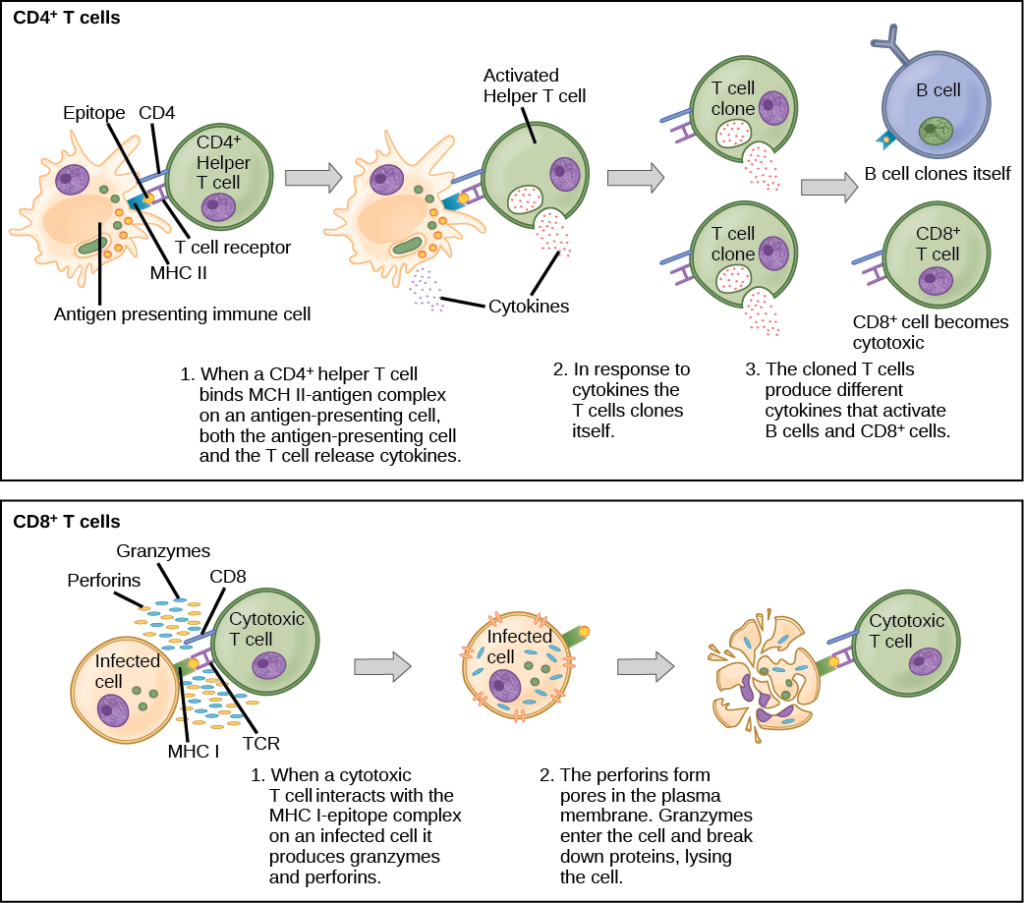
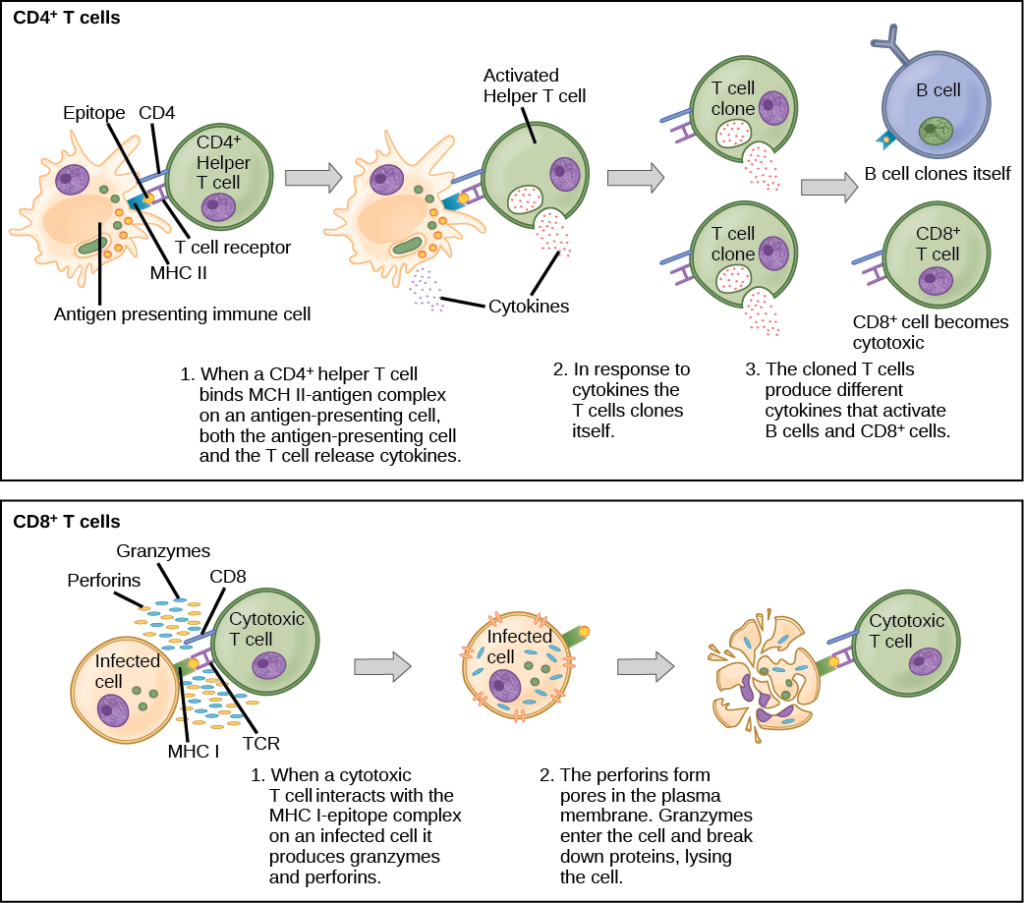


Figure 1. CD4+ T cells engage MHC II molecules on antigen-presenting cells (APCs) and become activated. Clones of the activated helper T cell, in turn, activate B cells and CD8+ T cells, which become cytotoxic T cells. Cytotoxic T cells kill infected cells (www.lumen.com).

B Lymphocytes

When stimulated by the TH2 pathway, naïve B cells differentiate into antibody-secreting plasma cells. A plasma cell is an immune cell that secrets antibodies; these cells arise from B cells that were stimulated by antigens.

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