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

**BY**

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**1.0 T-LYMPHOCYTES**

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, Jeremiah Bell, & Bhandoola, 2010](#_ENREF_67)). T lymphocytes 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, Murphy, & Sher, 1996](#_ENREF_1)). In this review, we focus on CD 4+ cells. Helper T cells (naïve CD4+ T lymphocytes) are triggered when they are presented with peptide antigens by MHC (major histocompatibility complex) class II molecules, which are expressed on the professional antigen-presenting cells (APCs) surface. Both are necessary for production of an adequate immune response ([Romagnani, 2006](#_ENREF_50)). T cells have on their surface T cell antigen receptors (TCR) responsible for recognition of an antigen/major histocompatibility complex (HLA complex), immunological accessory molecules identifying HLA determinants, and adhesion molecules recognizing their counterpart ligands on APCs ([Isakov, 1988](#_ENREF_23); [Kronenberg, Siu, Hood, & Shastri, 1986](#_ENREF_34)).

**2.0 B-LYMPHOCYTES**

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](#_ENREF_30)).

B cells represent mainly the humoral immunity. Nevertheless, their role as a cell itself is equally relevant. In practise, they are activated in patients with AITD ([Pyzik, Grywalska, Matyjaszek-Matuszek, & Roliński, 2015](#_ENREF_47)). In Graves’ Disease, B cells play a vital role as they are the source of pathognomonic activating autoantibodies (TRAb) against thyroid-stimulating hormone receptor (TSHR)([Ramos-Leví & Marazuela, 2016](#_ENREF_48)). TRAb, by binding to the receptor, chronically stimulates it. TSHR is expressed on thyroid follicular cells; thus, the consequence of this chronic stimulation is an increased production and secretion of thyroid hormones T4 and T3 ([Ajjan, Watson, & Weetman, 1996](#_ENREF_2); [Kristensen et al., 2015](#_ENREF_33)). Although the role of B cells in development of Hashimoto’s thyroiditis is not as significant as in GD, it should be mentioned that they produce autoantibodies to the thyroglobulin (Tg) and thyroid peroxidase (TPO), which are thyroid self-antigens ([Ramos-Leví & Marazuela, 2016](#_ENREF_48)). Antibody-dependent cell-mediated cytotoxicity is a meaningful factor responsible for apoptosis of thyroid follicular cells in HT.

**3.0 OSTEOMYELITIS**

Bone infection is called osteomyelitis. It is an acute or chronic inflammatory process involving the bone and its structures secondary to infection with pyogenic organisms, including bacteria, fungi, and mycobacteria. Interestingly, archeological finds showed animal fossils with evidence of bone infection, making this a relatively old disease.([Schmitt, 2017](#_ENREF_57)) Various terms were used to describe infected bone over the years until Nelaton came up with the term osteomyelitis in 1844.([Schmitt, 2017](#_ENREF_57)) Before the introduction of penicillin in the 1940s, management of osteomyelitis was mainly surgically consisting of extensive debridement, saucerization, and wound packing following which affected area is left to heal by secondary intention ([Schmitt, 2017](#_ENREF_57)) resulting in high mortality from sepsis. Since the availability of antibiotics, mortality rates from osteomyelitis, including staphylococcal osteomyelitis, has improved significantly.

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

T cells are the major cells of the adaptive immune system and are crucial mediators of the immune response. T cells originate and differentiate mainly into CD4 and CD8 T cells in thymus from lymphoid progenitor cells, which develop from hematopoietic stem cells in the bone marrow ([Haas, Pereira, & Tonegawa, 1993](#_ENREF_20); [Nguyen, Deng, Witherden, & Goldrath, 2019](#_ENREF_44)). A small proportion of T cells get differentiated into natural killer T cells (NKT) which function by eliciting immune responses mainly to pathogens, but are also implicated in autoimmunity and graft rejection ([Li et al., 2007](#_ENREF_37)).

Activated T cells express RANKL, which directly affects osteoclast precursor cells and induces the formation of osteoclast or osteoclastogenesis *in vitro*. In contrast, resting T cells have been reported to play a protective role in bone resorption. T cell deficient mice had no effect on RANKL mRNA expression, but the mice showed increased osteoclast numbers and reduced bone density ([Li et al., 2007](#_ENREF_37)). In an in vitro coculture of murine bone marrow cells, John et al. reported that though CD4 T cells had no effect on osteoclastogenesis, depletion of CD8 T cells led to a 40% increase in osteoclast formation ([John, Hock, Short, Glasebrook, & Galvin, 1996](#_ENREF_27)).

The inhibitory effect of resting T cells on osteoclast formation seems to be mediated through involvement of B cells, as depletion of CD4 and CD8 T cells in mice led to increased osteoclastogenesis by a mechanism that involved the complete suppression of OPG production by B cells ([Grčević, Lee, Marušić, & Lorenzo, 2000](#_ENREF_18)). Also, B cell deficient mice showed increased osteoclast formation and bone resorption, as these cells are the main OPG producing cells ([Li et al., 2007](#_ENREF_37)).

T cell infiltration has been implicated in various bone infection diseases as well as in autoimmune diseases, such as periodontitis and rheumatoid arthritis (RA). As bone loss occurs in these diseases and osteoclast-like cells were reported to be present at the site of infection, these data were strongly correlated to the role of osteoclasts in bone resorption ([Bromley & Woolley, 1984](#_ENREF_5); [Hao et al., 2015](#_ENREF_21)). Infection-induced activation of T cells leading to increased RANKL expression further contributed to increased osteoclast formation and bone resorption ([Colucci et al., 2007](#_ENREF_10)).

Cytokines produced by T cells also play a prominent role in bone physiology and metabolism. INF-γ, a major cytokine produced by T helper1 (Th1) cells, inhibits osteoclast formation and bone erosion along with IL-12 and IL-18, which induces Th1 cell differentiation ([Sato & Takayanagi, 2006](#_ENREF_55)). This was evident, as mice deficient in INF-γ receptor showed severe bone resorption in collagen induced arthritis ([Manoury-Schwartz et al., 1997](#_ENREF_41); [Takayanagi et al., 2000](#_ENREF_62)). Th2 cytokines, mainly IL-4 and IL-10 have also been reported to have an inhibitory effect on osteoclast formation([Sato et al., 2006](#_ENREF_54); [Takayanagi et al., 2000](#_ENREF_62)).

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

B cells are well known to act as antigen presenting cells (APCs) and differentiate into antibody secreting plasma cells upon encountering pathogens ([Ghia, Ten Boekel, Rolink, & Melchers, 1998](#_ENREF_17); [LeBien & Tedder, 2008](#_ENREF_36)). As the maturation and differentiation of B cells takes place in the bone marrow near bone cells, a complex interaction and crosstalk mechanism exists between the two, which affects their activity and function. Cytokines affecting bone metabolism, like TNF-α, IL-1 and IL-13, and vascular cell adhesion molecules, like molecules that are secreted by bone marrow stromal cells, directly affect B cell homing and differentiation ([Koni et al., 2001](#_ENREF_32)). Mice deficient in RANK or RANKL, the two major mediators of osteoclastogenesis, showed severe osteopetrosis along with reduced numbers of mature differentiated B cells secreting IgM and IgD in the lymph nodes and spleens, which could be related to reduced bone marrow cavities or altered stromal cells ([Kong et al., 1999](#_ENREF_31)). Immunomodulatory experimentation in mouse models altering RANKL/RANK/OPG pathways and interaction led to severe defects in B cell maturation and functions ([Yun et al., 2001](#_ENREF_68)). B cells expressed RANKL and differentiated into osteoclasts in the presence of M-CSF and RANKL during in vitro coculture ([Manabe et al., 2001](#_ENREF_40)). B cell depletion inhibited inflammatory bone loss in patients with RA. ([Coat et al., 2015](#_ENREF_9)). *P. gingivalis* infection in mice resulted in significant increase of B cell numbers as well as RANKL expression on B cells. Interestingly, this was not observed in B cell deficient *μ*MT mice, which were protected from infection-induced bone resorption ([Oliver‐Bell et al., 2015](#_ENREF_46)). In another report, *P. gingivalis* induced experimental periodontitis, adoptive transfer of regulatory B cells significantly inhibiting periodontal bone resorption. The inhibitory effects on bone loss by adoptive transfer were associated with reduced production of RANKL/OPG, TNF-α, and IL-1β, and increased IL-10 secretion ([Wang et al., 2017](#_ENREF_65)). A detailed analysis of circulating B cell subsets in severe periodontitis showed an increase of memory B cells, mainly class switched memory B cells. In addition, RANKL expression on B cells were increased, but the number of B cells with regulatory functions were decreased in severe periodontitis ([Demoersman et al., 2018](#_ENREF_15)). Altogether, these evidences suggest an important regulatory role of B cells in bone erosion, and therefore, B cells could be a potential therapeutic target for infection-induced bone loss.

**6.0 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 & Hochberg, 1997](#_ENREF_12)). 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, Dieppe, & Radin, 2008](#_ENREF_4)). 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 Smith et al., 2000](#_ENREF_35)), and this further leads to the release of matrix components, which elicit inflammatory mechanisms ([H. Jasin, 1988](#_ENREF_25)).

Even though osteoarthritis (OA) is mainly considered as a degradative condition of the articular cartilage, there is increasing body of data demonstrating the involvement of all branches of the immune system. Genetic, metabolic or mechanical factors cause an initial injury to the cartilage resulting in release of several cartilage specific autoantigens, which trigger the activation of immune response. Immune cells including T cells, B cells and macrophages infiltrate the joint tissues, cytokines and chemokines are released from different kind of cells present in the joint, complement system is activated, cartilage degrading factors such as matrix metalloproteins (MMPs) and prostaglandin E2 (PGE2) are released, resulting in further damage to the articular cartilage.

**7.0 INVOLVMENT OF T-LMYPHOCYTES IN THE PATHOGENESIS AND PROGRESSION OF OSTEOARTHRITIS**

Mononuclear cell infiltrates in synovial tissues have been reported in OA ([Haraoui, Pelletier, Cloutier, Faure, & Martel‐Pelletier, 1991](#_ENREF_22); [Kennedy, Plater-Zyberk, Partridge, Woodrow, & Maini, 1988](#_ENREF_29); [Lindblad & Hedfors, 1987](#_ENREF_38); [Sakkas et al., 1998](#_ENREF_53); [Smith, Triantafillou, Parker, Youssef, & Coleman, 1997](#_ENREF_60)) and have been shown to contain primarily CD3+ T cells ([Ishii et al., 2002](#_ENREF_24)). 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](#_ENREF_24)) and higher levels of Th1 cytokines, IL-2 and IFNγ, were detected in most of OA patients([Sakkas et al., 1998](#_ENREF_53)). 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, Yoshino, Kato, Tsuruha, & Nishioka, 1999](#_ENREF_43); [Scanzello, Sakkas, Johanson, & Platsoucas, 1999](#_ENREF_56); [ZWILLICH et al., 1994](#_ENREF_69)). 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](#_ENREF_3)). In another study OA chondrocytes were shown to stimulate autologous T cell response in vitro ([M Sakata et al., 2003](#_ENREF_51)). Cellular immunity to type III collagen and proteoglycan was detected after partial meniscectomy in rabbits([Champion & Poole, 1982](#_ENREF_7)). 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](#_ENREF_19)). 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](#_ENREF_13)). 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 ([Shen et al., 2011](#_ENREF_58)). 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., 2006](#_ENREF_42)).

**8.0 INVOLVMENT OF B-LMYPHOCYTES IN THE PATHOGENESIS AND PROGRESSION OF OSTEOARTHRITIS**

Cellular infiltrates in the inflamed OA synovium have been reported to contain activated B cells along with other cell types ([Revell, Mayston, Lalor, & Mapp, 1988](#_ENREF_49)). A clonal analysis of B cells in OA synovium revealed their oligoclonal nature suggesting an antigen driven activation instead of non-antigenic activation ([Shiokawa, Matsumoto, & Nishimura, 2001](#_ENREF_59)). 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 ([LÜTJEN-DRECOLL & BRUNE, 1988](#_ENREF_39)). Similarly, autoantibodies were found in OA patients against cartilage derived proteins osteopontin ([Masahiro Sakata et al., 2001](#_ENREF_52)), cartilage intermediate layer protein (CILP) ([J. i. Tsuruha et al., 2001](#_ENREF_64)), YKL-39, ([J.-I. Tsuruha et al., 2002](#_ENREF_63)), fibulin-4 ([Xiang et al., 2004](#_ENREF_66)) and collagen ([Charríre et al., 1988](#_ENREF_8)). Anti-CCP antibodies were detected in 7 out of 136 OA patients ([Du et al., 2005](#_ENREF_16)), while another group also detected them in OA patients but at significantly lower levels compared to RA patients ([Caspi et al., 2006](#_ENREF_6)). Antibodies against native G1 domain of aggrecan core protein were found in synovial fluid of OA patients ([Karopoulos, Rowley, Ilic, & Handley, 1996](#_ENREF_28)). Using proteomic approach, Xiang et al identified triosephosphate isomerase (TPI) as an important antigen with autoantibodies present specifically in OA but not in RA ([Xiang et al., 2004](#_ENREF_66)). Other studies have reported autoantibodies in animal models of OA including horses ([Niebauer, Wolf, Yarmush, & Richardson, 1988](#_ENREF_45)) and dogs ([De Rooster, Cox, & Bree, 2000](#_ENREF_14)). The role of the autoantibodies against cartilage components in development of OA has been further highlighted by studies showing their deposition ([Cooke, 1987](#_ENREF_11); [H. E. Jasin, 1985](#_ENREF_26)) and cytotoxic effects on cartilage ([Takagi & Jasin, 1992](#_ENREF_61)), which may be one of the mechanisms playing important role in cartilage degeneration in OA.

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