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

**By**

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1. **Introduction**

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 (Cano and Lopera, 2013).

**Osteomyelitis**

Osteomyelitis 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. It is a bone infection(Momodu and Savaliya, 2019).

Osteomyelitis encompasses a broad spectrum of disease mechanisms with three generally accepted categories: hematogenous (blood borne) spread, contiguous contamination and vascular or neurologic insufficiency associated infection (Lew and Waldvoge, 2004). The characteristics of each category can be summarized as follows:

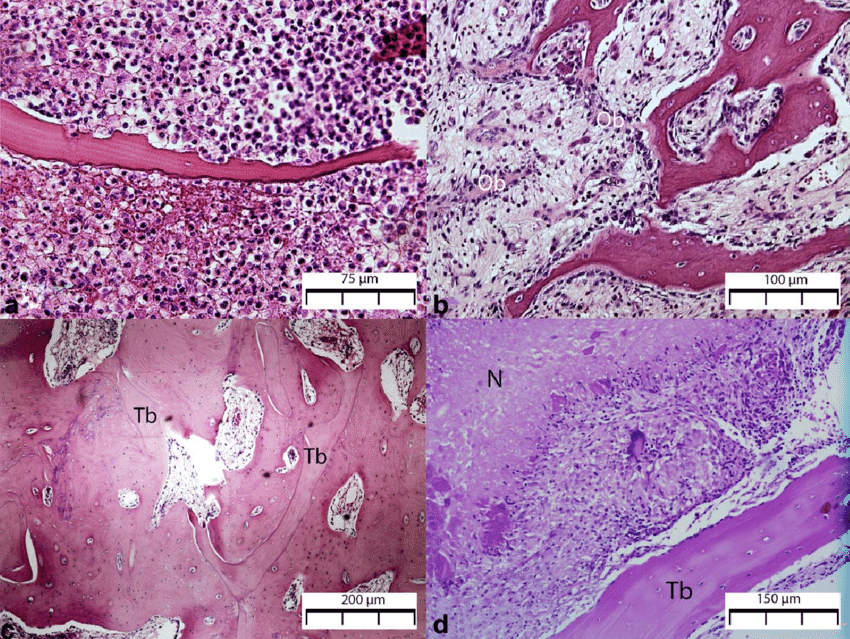
(1) Primary hematogenous spread of bacteria mainly afflicts the metaphysis of skeletally immature patients or vertebral bodies at all ages, although infection at other locations may occur (Paakkonen *et al.,* 2015; Francis *et al.,* 2016).

(2) Contiguous infection is usually spread from a contaminated site, most commonly seen with direct contamination of bacteria in open fractures or joint replacement surgery with an orthopedic implant (Rosenberg, 2010).

(3) Vascular or neurologic insufficiency associated osteomyelitis results from poor blood supply, diabetic wounds, loss of protective sensation and altered immune defenses, commonly affecting the lower extremity (SooHoo *et al.,* 2009; Yousefi *et al.,* 2015).

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Fig 1.0: A diagram showing three categories of osteomyelitis. (A and B) Primary hematogenous (blood borne) spread of bacteria mainly afflicts the vertebral bodies at all ages or the metaphysis of skeletally immature patients. (C and D) Contiguous bone infection is most commonly seen with direct contamination of bacteria in open fractures or joint replacement surgery with prosthetic implants. (E) Vascular or neurologic disease associated osteomyelitis most commonly affects the lower extremity (Birt *et al.,* 2016).



# Fig 1.1: Fresh tissue histology of osteomyelitis. Fresh, haematoxylin and eosin stained tissue sections. (a) The early phases of osteomyelitis are characterized by influx of inflammatory cells and bone necrosis. Note the centrally located necrotic/acellular bone trabecula lined by numerous Howship's lacunae. (b) The destruction of bone tissue prompts reactive deposition of bone tissue by osteoblasts (Ob), which is primarily of the woven type. (c) When infection subsides, reactive bone deposition may encase some of the necrotic trabeculae (Tb). This phenomenon is also referred to as " creeping substitution. " (d) The presence of necrotic granulomas (N) in this case of osteomyelitis suggested an infection with mycobacterium tuberculosis. Note the relative absence of bone tissue reaction in the adjacent trabecular bone (De Boer *et al.,* 2016),

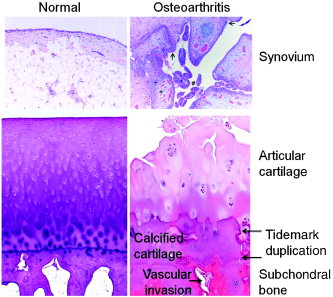
**Osteoarthritis**

Osteoarthritis is the clinical and pathological outcome of a range of disorders that results in structural and functional failure of synovial joints (Nkuki, 1999). Traditionally, it has been considered a disease of articular cartilage. The current concept holds that osteoarthritis involves the entire joint organ, including the subchondral bone, menisci, ligaments, periarticular muscle, capsule, and synovium (Hunter and Felson. 2006).

Osteoarthritis is the most prevalent form of arthritis, with an associated risk of mobility disability (defined as needing help walking or climbing stairs) for those with affected knees being greater than that due to any other medical condition in people aged 65 (Peach *et al.,* 2005). Osteoarthritis is a multifactorial process in which mechanical factors have a central role and is characterised by changes in structure and function of the whole joint (Martin and Buckwalter, 2001).There is no cure, and current therapeutic strategies are primarily aimed at reducing pain and improving joint function.

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Fig 1.2: Pathogenic features consistent with osteoarthritis (“joint failure”) (Hunter and Felson, 2006).



# Fig 1.3: Histologic features of osteoarthritis (OA). The normal synovium has a thin (1–2 cells thick) lining layer and a vascularized, loose connective tissue sublining layer. OA synovium demonstrates features of synovial villous hyperplasia (#), lining hyperplasia (arrows), increased vascularity (+), and perivascular mononuclear cell (inflammatory) infiltration. In OA articular cartilage, loss of cells and matrix is accompanied by areas of cell clusters. There is thickening of the calcified zone and duplication of the tidemark, which normally separates the articular cartilage from the underlying calcified cartilage. The subchondral bone is also thickened, and vascular invasion, which can extend through the tidemark and into the base of the articular cartilage, is seen. Images kindly provided by Ed DiCarlo, Hospital for Special Surgery, New York, NY. The image of the normal articular cartilage is reproduced, with permission, from Goldring SR, Goldring MB. Biology of the normal joint. In: Firestein GS, Budd RC, Harris ED Jr, McInnes IB, Ruddy S, Sergent JS, editors. Kelley's textbook of rheumatology. 8th ed. Philadelphia: Saunders Elsevier; 2009. p. 1–22 (Research gate, 2020).

**1.1 Involvement of T-lymphocytes in the pathogenesis and progression 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 vertebra (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.,* 1999). 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.

**1.2 Involvement of T-lymphocytes in the pathogenesis and progression of Osteoarthritis**

Analysis of enzyme-linked immunosorbent assay (ELISA) data has shown that compared with age-matched healthy controls, patients with OA show higher levels of the soluble form of CD4 (sCD4) in their serum. This suggests that peripheral T helper (Th) cells are involved in the pathogenesis of OA (Symons *et al.,* 1991). Similarly, when stimulated with phorbol myristate acetate (PMA) and ionomycin, peripheral mononuclear cells from OA patients showed a higher expression of CD4 and CD8 markers than their counterparts from healthy controls (Dolganiuc *et al.,* 1999). Indeed, the ratio of CD4+/CD8+ in the blood of OA patients is higher than that in the blood of healthy controls, although healthy controls and OA patients have fairly similar numbers of CD4+ and CD8+ T cells in their blood (Hussein *et al.,* 2008). Further evidence of the involvement of peripheral T cells in the pathogenesis of OA was provided by the discovery that the response to autologous chondrocytes of peripheral T cells isolated from OA patients is greater than of peripheral T cells isolated from controls and that this response is partially blocked by antibodies against human leukocyte antigen (HLA) classes I and II, CD4, and CD8 (Sakata *et al.,* 2003). Interestingly, T cells in a subset of OA patients were found to recognize the peptides representing amino acid regions 16–39 and 263–282 of human cartilage proteoglycan aggrecan (PG), and peripheral blood mononuclear cells from these PG-reactive OA patients showed an increased production of pro-inflammatory cytokines/chemokines in response to PG peptide stimulation (de Jong *et al.,* 2010). Based on these compelling findings, the autoimmune responses of peripheral T cells may aid understanding of immune-mediated mechanisms in OA.

Enzyme-linked immunosorbent assay analysis revealed higher levels of sCD4 not only in the peripheral blood but also in the synovial fluid of patients with OA, compared with age-matched healthy controls, which suggests that Th cells in the synovial fluid are involved in the pathogenesis of OA (Symons *et al.,* 1991). When stimulated with PMA and ionomycin, mononuclear cells from the synovial fluid of OA patients showed a high expression of CD4 and CD8 markers (Dolganiuc *et al.,* 1999). These compelling results suggested that T cells in the synovial fluid are associated with the pathogenesis of OA. This conclusion was supported by subsequent investigations. For example, the percentage of T cells in the synovial fluid of OA patients was found to be significantly higher than that in their peripheral blood (van de Putte *et al.,* 1975), and T cells in the synovial fluid of OA patients expressed class II HLA (an indicator of activated T cells) (Haynes *et al.,* 2002). The percentages of CD4+ and CD8+ cells in the synovial fluid of OA patients were even similar to those found in RA patients (Hussein *et al.,* 2008).

T cells are the major constituents of synovial infiltrates in the membranes of OA patients, and both CD4+ T cells and CD8+ T cells have been found within synovial aggregates (Haynes *et al.,* 2002). For example, synovial tissue extracted from OA patients displayed perivascular CD3+ T cell infiltration at an early stage (Nakamura *et al.,* 1999). Similarly, using immunohistochemical analysis, CD3+, CD4+, and CD8+ T cells were detected predominantly in the sublining layer and more limitedly in the deep layer of the synovium of patients with OA, whereas the presence of CD4+ T cells in the synovial sublining layer was detected more strongly in OA patients than in normal subjects (Ishii *et al.,* 2002). CD4+ T cells were found to be predominant among the T-cell infiltrates in the synovial tissue, and the number of CD4+ T cells was higher in the synovial sublining layer of patients with OA than in that of normal subjects. Indeed, the medial synovium of patients with knee OA has been shown to contain more CD4+ T cells than the lateral synovium (Saito et al. 2002). Interestingly, synovial aggregates from OA patients express CD80, an inducible costimulatory ligand involved in T-cell activation (Haynes *et al.,* 2002; Sanders *et al.,* 1988), suggesting that synovial aggregates in OA patients are areas of antigen recognition and T-cell activation. Similarly, researchers investigating 30 patients with OA found CD3+ T cell aggregates in the synovial membrane in 65% of the patients, and the activation antigens CD69, CD25, CD38, CD43, CD45RO, and HLA class II were also found in the synovial membrane (Sakkas *et al.,* 1998). In addition, HLA-antigen D-related (DR)-expressing T cells were found in the synovial membranes of OA patients using immunohistochemical analysis, although to a lesser degree than in RA patients (Johnell *et al.,* 1985). The conclusion that activated T cells are aggregated in the synovial membranes of OA patients was further supported by the discovery that virtually all T cells in OA joints express activation markers, such as HLA-DR and CD69 (Yamada *et al.,* 2011). Interestingly, OA patients older than 75 have higher percentages of CD3+, CD4+, and CD8+ cells in their synovial membranes than OA patients younger than 75 (Pawlowska *et al.,* 2009). This may suggest that age is among the risk factors for OA.

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

**Th1 and OA**

Under the stimulation of interleukin (IL)-12, naïve CD4+ T cells differentiate into Th1 cells, which produce IL-2, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, lymphotoxins, and granulocyte-macrophage colony-stimulating factor ( Chen and Kolls, 2013; Raphael *et al.,* 2014; Ren *et al.,* 2017). Most current evidence indicates that Th1 cells do not alter significantly on entering the peripheral blood of OA patients. For example, flow cytometry analysis has shown that there is little difference in the percentage of circulating Th1 cells (CD4+IFN-γ+ T cells) between OA patients and healthy controls (Zhang *et al.,* 2011). Similarly, no variation in either the percentage or the absolute number of circulating Th1 cells (CD4+IFN-γ+ T cells) has been found between patients with OA and healthy controls (Zhang *et al.,* 2012). However, in a study with 25 OA patients and 13 healthy controls, the number of circulating Th1 cells (IFN-γ+CD4+CD8− T cells) and the level of serum IFN-γ were found to *etbe* significantly higher in patients with OA than in healthy controls (Qi *et al.,* 2016). The difference in the markers (CD4+IFN-γ+ vs. IFN-γ+CD4+CD8−) used in the two studies to define Th1 cells may account for this discrepancy. Another explanation may lie in the variation between OA patients, such as differences between the stages of OA. The alteration of the Th1 cell profile in the peripheral blood of OA patients thus requires further investigation.

In contrast with the findings for peripheral blood, the synovial fluid of OA patients shows an increase in Th1 cells. Although early experiments suggested that the concentrations of IL-2, IFN-γ, and TNF-β in the synovial fluid of OA patients are below the limit of detection by ELISA analysis (Dolhain *et al.,* 1996), reverse transcription polymerase chain reaction (RT-PCR) analysis has since revealed that cells from the synovial fluid of OA patients express IL-2 and IFN-γ when stimulated with PHA and ionomycin (Haynes *et al.,* 2002). Indeed, intracellular IFN-γ has been detected at higher levels in both CD4+ and CD8+ cells from the synovial fluid than in the peripheral blood of OA patients (Dolganiuc *et al.,* 1999). In addition, high concentrations of IL-1β and TNF-α have been observed in the synovial fluid of patients with OA, whereas these markers are below the limit of detection in healthy subjects (Hussein *et al.,* 2008).

Th1  cells can also be found in the synovial membranes of OA patients. For example, IL-2, IFN-γ, and their receptors are usually detected in the synovial membranes of OA patients (Sakkas *et al.,* 1998; Dolhain *et al.,* 1996). Similarly, INF-γ+ cells have been detected in the synovial membranes of patients with OA, predominantly in the sublining layer of the synovium, although to a lesser degree than in RA patients (Ishii *et al.,* 2002). In a mouse model of OA induced by anterior cruciate ligament transection (ACLT), the expression of IFN-γ increased during OA onset (30 days after ACLT) and then decreased at a later stage of OA (90 days after ACLT) (Shen *et al.,* 2011). Most importantly, a well-designed study showed that Th1 cells are predominant in both OA and RA joints (Yamada *et al.,* 2011). Indeed, the number of IFN-γ+ cells in the synovium of patients with OA is approximately five times greater than that of IL-4+ cells (Ishhi *et al.,* 2002).

In summary, although the profile of Th1 cells in the peripheral blood requires further analysis, Th1 cells have been shown to accumulate in the synovial fluid and synovial membranes of OA patients, which suggests that Th1 cells play important roles in the pathogenesis of OA. In addition, Th1 cell responses in the synovial fluid and synovial membranes of OA patients may be a marker of OA disease activity.

**Th2 and OA**

When stimulated by IL-4, naïve CD4+ T cells differentiate into Th2 cells (Ren *et al.,* 2017).Through the production of IL-4, IL-5, IL-10, and IL-13, Th2 cells affect the function of B cells, dendritic cells, eosinophils, etc. and play important roles in the host’s defense against multicellular parasites and in the pathogenesis of allergies (Chen *et al.,* 2015; Raphael *et al.,* 2014; Chapvoal *et al.,* 2010; Vahedi *et al.,* 2013; Ren *et al.,* 2016). Most recent studies have shown that Th2 cells undergo limited alteration in the peripheral blood, synovial fluid, and synovial membranes of OA patients. For example, in a study of 18 OA patients, the IL-10 transcript was found in nearly all of the patients using competitive PCR analysis, whereas IL-4 and IL-5 were not detected in the synovial membranes of any of the patients (Sakkas *et al.,* 1998). Similarly, the concentrations of IL-4 and IL-10 in the synovial fluid were below the limit of detection by ELISA analysis (Partsch *et al.,* 1998). Using flow cytometry analysis, low concentrations of Th2 cytokines such as IL-4 and IL-10 were detected in both the synovial fluid and the peripheral blood of OA patients (Dolganiuc *et al.,* 1999)Although cells from the synovial fluid of OA patients stimulated with PHA and ionomycin expressed IL-10 at 48 h poststimulation, no signal for IL-4 was detected by RT-PCR analysis (Haynes *et al.,* 2002)The observed expression of IL-10 in OA patients’ synovial membranes or synovial fluid cells may come from other cells, such as regulatory T cells (Treg cells).

Together, although these compelling findings suggest that Th2 responses play only a limited role in the pathogenesis of OA, further strong evidence is needed to support this hypothesis.

**Th9 and OA**

Th9 cells, recently defined as subsets of Th cells, preferentially produce IL-9 (Ren *et al.,* 2017; Pan *et al.,* 2013; Zhao *et al.,* 2013; Schmitt *et al.,* 2014). Th9 cells facilitate immune responses against melanoma and intestinal worms and are closely associated with the immunopathology of allergic and autoimmune responses, such as systemic lupus erythematosus (SLE), experimental autoimmune encephalitis, and systemic sclerosis (Pan *et al.,* 2013; Zhao *et al.,* 2013; Schmitt *et al.,* 2014).

Th9 cells are also involved in the pathogenesis of arthritis. For example, a high level of IL-9 has been detected in the peripheral blood and synovial fluid of patients with RA and patients with psoriatic arthritis (PsA), and the level of IL-9 in the synovial fluid is higher than that in the peripheral blood for RA and PsA patients (Kundu-Raychaudhuri e*et al.,* 2016)Similarly, activated CD3+ T cells from the peripheral blood and synovial fluid of patients with PsA or RA produce high levels of IL-9 (Kundu-Raychaudhuri *et al.,* 2016). These results suggest that Th9 cells play critical roles in the pathogenesis of RA and PsA. Indeed, Th9 responses have also been observed in OA. For example, a high level of IL-9 has been detected in the peripheral blood and synovial fluid of OA patients, and the activation of purified CD3+ cells from the peripheral blood and synovial fluid of patients with OA produces a high level of IL-9, although lower than that observed in RA or PsA patients (Kundu-Raychaudhuri *et al.,* 2016).Even more importantly, in a study with 25 OA patients and 13 healthy controls, the number of circulating Th9 cells and serum IL-9 level were found to be significantly higher in OA patients than in healthy controls (Qi *et al.,* 2016). This study also found that the number of circulating Th9 cells was positively associated with the level of C-reactive protein in OA patients and that both the number of Th9 cells and the level of serum IL-9 were positively correlated with OA index (Qi *et al.,* 2016).

In summary, these well-designed experiments lead to the conclusion that Th9 cells significantly shape the pathogenesis of OA, as well as that of RA and PsA; however, the Th9 response in the synovial membranes of OA patients needs further investigation. In addition, serum IL-9 or the number of circulating Th9 cells may be a marker of OA disease activity.

**Th17 and OA**

Th17  cells secrete IL-17A (also known as IL-17), IL-17F, IL-21, and IL-22. Transform growth factor (TGF)-β, IL-6, IL-1β, and IL-23 have been reported to promote the differentiation of Th17 cells (Ivanov *et al.,* 2007; Wilson *et al.,* 2007; McGreachy *et al.,* 2008; Shabgah *et al.,* 2014; Floss *et al.,* 2015). Th17 cells provide protection against bacterial infection and are associated with the development of autoimmune diseases *via* the recruitment of cells in the granulocyte lineage, especially neutrophils (Miosssec *et al.,* 2012; Ren *et al.,* 2016; Ren *et al.,* 2016; Xiao *et al.,* 2016).Early investigations indicated that neither the percentages of circulating pure Th17 cells (CD4+IFN-γ−IL-22−IL-17+ T cells) and Th17 cells (CD4+IL-17+ T cells) nor the level of serum IL-17 differed significantly between OA patients and healthy controls (Zhang *et al.,* 2011). Similarly, no variation in the percentage or absolute number of circulating Th17 cells or the IL-17 plasma level was found between patients with OA and healthy controls (Zhang *et al.,* 2012). These findings indicated that little alteration occurs in the Th17 cell profile in the peripheral blood of OA patients. However, later observations suggested otherwise. In a rat model of OA induced by the injection of papain and l-cysteine into the right knee joint, the OA rats were found to have a higher serum IL-17 level than the control rats (Guoo *et al.,* 2015). In addition, in a study with 25 OA patients and 13 healthy controls, the number of circulating Th17 cells and the level of serum IL-17 were found to be significantly higher in patients with OA than in healthy controls (Qi *et al.,* 2016). As in the case of Th1 cells, variation in the markers used to define Th17 cells (CD4+IL-17+ vs. IL-17+CD4+CD8−) and the patients selected for investigation (e.g., diagnosis standard, disease index, patients’ background) may account for this discrepancy. These controversial findings regarding Th17 cell profile in the peripheral blood of OA patients suggest that the roles of circulating Th17 cells in the pathogenesis of OA need further investigation. Nevertheless, it is widely accepted that Th17 cells are present in the synovial fluid and synovial membranes of OA patients. For example, in addition to the strong expression of IL-17 mRNA in the synovial membranes of OA patients (Chabaud *et al.,* 1999),a high level of IL-17 has been measured in the synovial fluid of OA patients, whereas both are below the limit of detection in healthy subjects (Hussein *et al.,* 2008; Sarkar *et al.,* 2017). In addition, Th17 cells have been detected in the joints of OA patients, albeit in smaller numbers than in RA joints (Yamada *et al.,* 2011).

Collectively, these interesting results demonstrate the accumulation of Th17 cells in the synovial fluid and synovial tissue of OA patients; however, the exact role of Th17 cell response in the biology of OA needs further investigation.

**Th22 and OA**

Originally, IL-22 was regarded as a product of Th17 cells; however, recent evidence has indicated that a distinct subset of human skin CD4+ T cells (Th22) produces IL-22 but not IL-17 or IFN-γ (Trifari *et al.,* 2009). Increasing evidence has been provided for the involvement of Th22 cells in the biology of RA. For example, the percentage of Th22 cells is higher in RA patients than in healthy controls, and the percentage of Th22 cells is positively correlated with IL-22 expression in RA patients (Zhang *et al.,* 2011). In addition, the percentage of Th22 cells is positively correlated with both C-reactive protein levels and joint disease activity scores in RA patients (Zhang *et al.,* 2011). These compelling discoveries indicate that Th22 response is associated with the pathogenesis of RA and that blocking IL-22 expression may be a reasonable therapeutic strategy for RA. Th22 cells are also involved in the biology of ankylosing spondylitis. Similar to the results for RA, the percentage and absolute number of circulating Th22 cells were found to be elevated in patients with ankylosing spondylitis compared with healthy controls (Zhang *et al.,* 2012). Similarly, ELISA analysis revealed that the level of IL-22 in the plasma was higher in patients with ankylosing spondylitis than in healthy controls (Zhang *et al.,* 2012). However, Th22 cells seem to play a limited role in the pathogenesis of OA. For example, compared with healthy controls, OA patients show no change in the percentage of circulating Th22 cells (CD4+IFN-γ−IL-17−IL-22+ T cells) and the level of IL-22 in the plasma (Zhang *et al.,* 2011). Similarly, another independent experiment revealed that neither the percentage nor the absolute number of circulating Th22 cells, nor the plasma level of IL-22, differ between patients with OA and healthy controls (Zhang *et al.,* 2012).

Collectively, unlike RA and ankylosing spondylitis, OA involves only a limited alteration of Th22 response in the peripheral blood; however, we lack data on the Th22 profile in the synovial fluid and synovial tissue of OA patients.

**Treg Cells and OA**

Under the influence of TGF-β, naïve T cells differentiate into Treg cells, which produce IL-10 and TGF-β (Raphael *et al.,* 2014; Hori *et al.,* 2003; Bommireddy *et al.,* 2007; Carrier *et al.,* 2007). Treg cells are important immunoregulators in many inflammatory and autoimmune diseases, as they modulate the secretion of anti-inflammatory cytokines and the expression of receptors for cytokines (Miyara *et al.,* 2007). For example, RA patients have a lower percentage of Treg cells at sites of synovial inflammation and in the peripheral blood (Yudoh *et al.,* 2000), which may induce the downregulation of T-cell tolerance and exacerbate the inflammatory process. Increasing evidence has been provided that the profile of Treg cells in the peripheral blood, synovial fluid, and synovial membranes of OA patients is similar to that of RA patients. For example, the percentage and absolute number of Treg cells (CD4+CD25+/highCD127−/low) in the peripheral blood, synovial fluid, and synovial membranes are similar in RA patients and OA patients, and Treg cells in both cases show greater accumulation in the synovial fluid and synovial membranes than in the peripheral blood (Moradi *et al.,* 2014). In addition, Treg cells in the peripheral blood, synovial fluid, and synovial membranes of both OA patients and RA patients display a memory phenotype (CD45RO+RA−) (Moradi *et al.,* 2014). Neither does the activation status (CD69 and CD62L) nor the expression of markers associated with Treg function (CD152, CD154, CD274, CD279, and GITR) in the peripheral blood, synovial fluid, or synovial membranes differ between OA patients and RA patients (Moradi *et al.,* 2014). Those compelling results indicate that as in the case of RA, a decrease in Treg-cell responses is involved in the pathogenesis of OA. Indeed, Ponchel et al. (Poncheal *et al.,* 2015), analyzed blood from 121 healthy controls and 114 OA patients and found that the OA patients had fewer Treg cells than the healthy controls after adjusting for age (Poncheal *et al.,* 2015). Although the frequency of CD4+CD25+Foxp3+ Treg cells has been found to be elevated in the blood of OA patients, OA patients show lower IL-10 secretion from Treg cells and fewer Tim-3+ Treg cells in the blood (Li *et al.,* 2016). Similarly, in a rat model of OA induced by the injection of papain and l-cysteine into the right knee joint, the percentage of CD4+CD25+Foxp3+ Treg cells in the peripheral blood was significantly lower in the OA rats than in the control rats (Guo *et al.,* 2015).

In summary, a decrease in Treg-cell response may be involved in the pathogenesis of OA; however, the alteration of Treg-cell responses in the peripheral blood, synovial fluid, and synovial membranes of OA patients requires more comparative investigation with age-matched healthy controls.

**Follicular Helper T (Tfh) Cells and OA**

Follicular helper T cells, located in the follicles of lymphoid tissue, induce B cells to produce immunoglobulins (Ueno *et al.,* 2015). Tfh cells express various distinguishing genes, such as CXCR5, PD-1, ICOS, CD40L, Bcl-6, and IL-21 (Crotty, 2011). Increasing evidence has been provided for the influence of Tfh cells on the severity of autoimmune diseases, such as SLE and RA. For example, the number of circulating Tfh cells (CXCR5+ICOS+CD4+ cells or CXCR5+PD-1+CD4+ cells) has been shown to increase in a subset of SLE patients in line with the diversity and concentration of autoantibodies and SLE severity (Simpson *et al.,* 2010). Similarly, immunohistochemistry analysis has revealed specific staining for CD4, CXCR5, and ICOS on infiltrating immune cells in the synovial tissues of RA patients, and the presence of Tfh cells (CD4+CXCR5+ICOS+ T cells) in the synovial tissues of RA patients has been verified using both triple-fluorescence immunostaining and confocal laser scanning (Chu *et al.,* 2014). This study provided evidence of the presence of Tfh cells in both SLE and RA patients, indicating the potentially important roles played by Tfh cells in the pathogenesis and progression of both diseases. However, the results of immunohistochemistry analysis, triple-fluorescence immunostaining, and confocal laser scanning revealed that Tfh cells are absent from the synovial tissues of OA patients (Chu *et al.,* 2014). Yet, a recent investigation demonstrated the importance of Tfh cells to the pathogenesis and progression of OA. In the latter study, the frequency of ICOS+, PD-1+, and IL-21+ CXCR5+CD4+ T cells in the peripheral blood of 40 patients with OA and 13 healthy controls was examined by flow cytometry, and the concentration of serum IL–21 was also determined. Compared with the healthy controls, the OA patients showed higher percentages of CXCR5+CD4+, PD-1+CXCR5+CD4+, ICOS+CXCR5+CD4+, and IL-21+CXCR5+CD4+ T cells (Shan *et al.,* 2017). Shan et al. (Shan *et al.,* 2017), also found that OA patients exhibited higher levels of serum IL-21 than healthy controls and, even more importantly, that the expression of IL-21+Tfh cells in OA patients was positively correlated with the disease activity of OA (Shan *et al.,* 2017). The latter study suggests that Tfh cells play a critical role in the pathogenesis and progression of OA. However, further well-designed research is needed to characterize Tfh cell profile in the peripheral blood, synovial fluid, and synovial membranes of OA patients.

**Cytotoxic T Cells and OA**

The peripheral blood of OA patients has been analyzed using flow cytometry, revealing that patients with OA have significantly fewer CD8+ T cells and a higher CD4+:CD8+ ratio than healthy subjects (Kuryliszyn-Moskal, 1995). However, patients with OA have normal proportions of CD8+CD45RA+, CD8+CD29+, and CD8+S6F1+ cells in both their peripheral blood and their synovial fluid (Sohen *et al.,* 1991). These results indicate the alteration of peripheral CD8+ T cells in OA patients. Although CD8+ T cells can be found in the synovial membranes of OA patients, the major component of the T-cell infiltrate cannot. Most of the T cells found in the synovial membranes of patients with OA are helper T cells, whereas cytotoxic T cells occur sparsely in patients with OA (Redboard and Osial 1987). Similarly, fewer CD8+ T cells than CD4+ T cells have been found in the lining, the sublining, and even the deep layer of the synovium of patients with OA (Ishii *et al.,* 2002). In addition, although both CD4+ and CD8+ T cells have been found in the synovial aggregates of OA patients, the aggregates contain a larger proportion of CD4+ T cells than of CD8+ T cells, and the CD8+ T cells are often located toward the periphery of the aggregates (Haynes *et al.,* 2002). CD8+ T cells play an important role in the pathogenesis of OA, although they are not the predominant T-cell type found in the synovial aggregates of OA patients. In mice with ACLT-induced OA, CD8+ T cells were activated once OA had been initiated, and the percentage of activated CD8+ T cells was significantly higher in the ACLT group than in the sham group during OA progression (Hsieh *et al.,* 2013). In addition, the number of CD8+ T cells expressing tissue inhibitor of metalloproteinase-1 (TIMP-1) was found to be correlated with OA severity and inhibiting the expression of TIMP-1 in the joints retarded the progression of OA (Hsieh *et al.,* 2013). Cartilage degeneration occurred more slowly in CD8+ T cell knockout mice than in wild-type mice (Hsieh *et al.,* 2013).

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

**T Memory (Tm) Cells and OA**

Once activated, most T cells undergo apoptosis; however, a minority persist as Tm cells. An increasing number of researchers have begun to investigate the profile of Tm cells in the pathogenesis of OA. For example, although healthy individuals showed no difference in the percentages of CD45RO+CD4+ T cells and CD45RA+CD4+ T cells in the peripheral blood, more CD45RO+ cells than CD45RA+ cells were found in the peripheral blood of patients with OA (Ezawa *et al.,* 1997). In patients with OA, the majority of CD4+ T cells in the synovial fluid and synovial tissue are CD45RO+ and CD45RA−, suggesting that an accumulation of CD45RO+ memory CD4+ T cells is a generalized phenomenon in OA joints (Ezawa *et al.,*1997). Similarly, a study with 25 OA patients and 13 healthy controls revealed that the number of circulating CD4+CD45RO+ T cells was significantly higher in patients with OA than in healthy controls (Qi *et al.,* 2016). Other evidence for the possible involvement of Tm cells in the pathogenesis of OA includes the detection of the regulated on activation, normal T cell expressed, and secreted chemokine (a potent chemoattractant for leukocytes, such as CD45RO+ memory T cells) and CD29 (a 1 integrin expressed by Tm cells) in the synovial fluid of OA patients (Haynes *et al.,* 2002; Sanders *et al.,* 1988; Volin *et al.,* 1988)

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

**Unconventional T Cells and OA**

Recent investigations have also highlighted the involvement of unconventional T cells in the pathogenesis of OA. For example, more and more evidence has been provided that γδ T cells are involved in the pathogenesis of RA. For example, the number of γδ T cells has been found to increase in the synovial membranes of RA patients (Mathieu *et al.,* 1981; Andreu *et al.,* 1991; Jacobs *et al.,* 1992; Meliconi *et al.,* 1992), and γδ T cells in the synovial membranes have more and/or more avid Fc receptors for immunoglobulin G IgG in patients with RA compared with controls (Mathieu *et al.,* 1981). Further research has shown that the majority of synovial γδ T cells in RA patients do not express Vγ9, Vδ2, or Vδ1-Jγδ1 (Andreu *et al.,* 1991). However, most recent studies have indicated that the number of γδ T cells in the synovial membranes of patients with OA does not increase (Andreu *et al.,* 1991; Jacobs *et al.,* 1992; Meliconi *et al.,* 1992). Immunohistochemical staining of synovial tissue with early-stage OA shows T-cell infiltration in the perivascular area, with the clonality of restricted T cell receptor usage in the V beta chain (Nakamura *et al.,* 1999), which also indicates the minimal alteration of γδ T cells in OA patients. Recent studies have shown that the synovial membranes of OA patients express CD1 (Cauli *et al.,* 2000), which presents non-protein antigens to NKT cells, suggesting that CD1-restricted T cells may play a role in the pathogenesis of OA.

Overall, although numerous studies of the involvement of conventional T cells in OA have been conducted, it will be useful to determine the importance to OA of unconventional T cells such as CD1-restricted T cells, MR1-restricted mucosal-associated invariant T cells, major histocompatibility complex class Ib-reactive T cells, and γδ T cells (Godfrey *et al.,* 2015).

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Fig 1.4: **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 (Li *et al.,* 2017).

Mononuclear cell infiltrates in synovial tissues have been reported in osteoarthritis (Smith *et al.,* 1997; Lindblad and Hedfors, 1987; Sakkas *et al.,* 1988; Kennedy *et al.,* 1988; Harraoui *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 osteoarthritis 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 osteoarthritis patients (Sakkas *et al.,* 1988). T-cells in lymphocytic aggregates in osteoarthritis 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 osteoarthritis patients. Analysis of α/β T cell receptor diversity revealed the presence of oligoclonal populations of T cells in osteoarthritis 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 osteoarthritis, several candidate antigens have been proposed. T cells derived from peripheral blood and synovial fluid of osteoarthritis patients showed a strong response to autologous chondrocyte and fibsroblast membrane preparations (Alsalameh *et al.,* 1990).

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

As most bone infections are caused by extracellular pathogens, and the primary mechanism by which the host clears them is via phagocytosis of antibody-opsonized bacteria, the humoral immune response mediated by B-cells is critical. In recognition of this, several research groups have performed experiments to characterize the antibody-mediated immune response and identify those proteins that are immunogenic in S. aureus biofilm infections (Li *et al.,* 2008; Brady *et al.,* 2006). In these animal studies, sera were collected prior to infection, and at subsequent time points thereafter, and used to characterize the Ig response, and identify novel immunodominant antigens. Infection of naïve mice results in an initial IgM response in the first week, followed by a very specific IgG2b response at 2 weeks (Li *et al.,* 2008). Western blot assays on bacterial extracts separated by two-dimensional gel electrophoresis revealed humoral immunity against several bacterial antigens, including cell surface-associated beta-lactamase, lipoprotein, lipase, autolysin, and an ABC-transporter lipoprotein (Brady *et al.,* 2006). As a result of this work, several vaccine trials are currently underway. One of the most challenging forms of osteomyelitis to treat is MRSA infection of total joint replacements (Darouiche, 2004). As this patient population is typically >65 years of age, and are poor candidates for active immunization with purified bacterial products, several groups are proposing a potential passive immunization strategy to prevent reinfection following revision surgery. The attraction of this approach is that protective humoral immunity could be achieved 2 weeks prior to surgery by infusing the patient with protective monoclonal antibodies (mAbs). Our efforts in this regard have focused on antiautolysin (Alt) mAb, that targets both the aminidase (Amd) and the glucosaminidase (Gmd) subunits of the S. aureus enzyme. Alt is one of the catalytically distinct peptidoglycan hydrolases in S. aureus that is required to digest the cell wall during mitosis (Baba and Schneewind, 1998). Scanning electron microscopy studies have demonstrated that in addition to being an essential gene for growth, antiAlt antibodies bound to S. aureus during binary fission localize to regions of the bacteria that are not covered by the cell wall (Yamada *et al.,* 1996). Furthermore, Alt is also known to be an adhesion (Heilmann *et al.,* 2005; Hilmann *et al.,* 1997), thus antiAlt mAb may have protective effects via multiple mechanisms of action including:

(1) inhibition of mitosis,

(2) mAbmediated serum lysis via complement binding to naked periplasm,

(3) opsonization, and

(4) inhibition of bacterial attachment to host tissue.

Future studies designed to evaluate these mechanisms and the protection of these mAb in vivo will determine the potential of passive immunization as a therapeutic option to prevent bone infection in orthopaedic patients.

**1.4 Involvement of B-lymphocytes 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 *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.,* 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.,* 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 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 (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, 2005; 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.

Conclusion

The T-lymphocytes and B-lymphocytes play a key role in the pathogenesis and progression of osteomyelitis and osteoarthritis.

Intracellular persistence of the pathogen (Staphylococcus aureus) within the host osteoblast in chronic osteomyelitis cases has been identified. Although biofilm formation on devitalized tissue is the main cause of the clinical quiescence of chronic osteomyelitis, intracellular pathogens may also have a role at some point in the pathogenesis of this disease. This finding may lead to the development of new modalities to treat chronic osteomyelitis (Webb *et al.,* 2007; Ellington *et al.,* 2006).

Osteoarthritis (OA) is the most common joint disorder, is associated with an increasing socioeconomic impact owing to the ageing population and mainly affects the diarthrodial joints

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