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**The Involvement Of T and B Lymphocytes In The Pathogenesis and Progression of Osteomyelitis and Osteoarthritis**

**Osteomyelitis**

The definition of osteomyelitis is generally accepted as an inflammatory process of bone and bone marrow caused by an infectious organism(s) which results in local bone destruction, necrosis and apposition of new bone ([Kumar, Abbas *et al.,* 2014](#_ENREF_1); [Lew and Waldvogel 1997](#_ENREF_2); [Mouzopoulos, Kanakaris *et al.,* 2011](#_ENREF_3)) The term osteomyelitis implies bone or joint infection. Although bone is normally resistant to bacterial colonization, events such as trauma, surgery, the presence of foreign bodies, or the placement of prostheses may disrupt bony integrity and lead to the onset of bone infection. Osteomyelitis can also result from hematogenous spread after bacteremia. When prosthetic joints are associated with infection, microorganisms typically grow in biofilm, which protects bacteria from antimicrobial treatment and the host immune response. Symptoms may include pain in a specific bone with overlying redness, fever, and weakness. 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.

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

Treatment often involves both antimicrobials and surgery. In those with poor blood flow, amputation may be required. Treatment outcomes are generally good when the condition has only been present a short time. About 2.4 per 100,000 people are affected a year. The young and old are more commonly affected. Males are more commonly affected than females.( Ferri et al .,2017)The condition was described at least as early as the 300s BC by Hippocrates. Before the availability of antibiotics the risk of death was significant(Brackenridge et al .,2016)

T cell activation is invariably associated with virus infections, but activation of T cells is also noted, for example, in patients with persistent bacterial infections with intracellular pathogens or localised bacterial biofilms. The latter is characterised by a destructive inflammatory process. Massive infiltration of leukocytes, predominantly of polymorphonuclear neutrophils (PMNs) and of T lymphocytes, is seen. While PMN influx into sites of bacterial infection is in line with their role as “first-line defence” a role of T cells in bacterial infection has not yet been delineated. We now found evidence for activation and expansion of peripheral blood T cells and an upregulation of Toll-like receptors 1, 2, and 4 on small portions of T cells. T cells recovered from the infected site were terminally differentiated and produced interferon gamma, a cytokine known to enhance functions of phagocytic cells, leading to the conclusion that infiltrated T cells support the local immuner defence.

**Introduction**

Activation and expansion of T lymphocytes is invariably associated with the immune response to virus infection, and the clearance of virus-infected cells. Activation of T cells, however, is also seen in bacterial infection, particularly in those caused by intracellular bacteria (J. T. Harty *et al.,* 2000)and—as we showed recently—in patients with implant-associated osteomyelitis, a prototype of a biofilm infection (C. Wagner *et al .,* 2006)

Bacterial biofilms are increasingly recognised as the cause for persistent and destructive inflammatory processes (J. W. Costerton *et al.,* 1999) . According to Donlan and Costerton (R. M. Donlan *et al .,* 2002)biofilms are defined as “microbial derived sessile communities characterised by cells that are irreversibly attached to a substratum or interface or to each other, embedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription.” It is generally assumed that bacteria in biofilms escape the host defence. In vitro data suggest that bacteria in biofilms as not as susceptible to the phagocytic effector functions as their planktonic living counterparts ( J. G. Leid *et al .,* 2002)there is, however, no doubt that biofilms are not entirely protected (F. Günther *et al .,* 2009)and that biofilm infection elicit an activation of the immune response with an infiltration into the infected site of leukocytes, predominantly of polymorphonuclear neutrophils (PMNs) and T lymphocytes(F. Zimmermann *et al .,* 2013)

While the participation of PMN in the defence against bacterial infection and in the acute inflammatory response is well understood, a role for T cells has not yet been delineated, nor is it known how T cells recognise bacteria. In that context, the aim of the present study was to analyse T cells of patients with persistent bacterial infections with regard to expression of activation-associated receptors on T cells, particularly of Toll-like receptors (TLRs) on. TLRs recognise conserved microbial structures including lipopolysaccharides (LPSs), lipoteichoic acid (LTA), lipopeptides, or bacterial DNA and RNA. As the so-called “pattern recognition receptors” TLRs are primarily studied on cells of the innate immune response; however, TLR are also detected on T cells, and a modulatory function of the specific, adaptive immune response via TLRs is presumed ( T. Imanishi et al .,2007).We focussed on TLR1, TLR2, and TLR4, because these receptors alone or in combination recognise the bacterial products LTA or LPS which might be present at the site of infection. Moreover, to further characterise T cells we determined surface receptors known to be associated with activation, such as CD11b and CD57, as well as production of interferon gamma, a cytokine known for its capacity to activate phagocytic cells.

**Osteoathritis**

Osteoarthritis occurs when the cartilage that cushions the ends of bones in your joints gradually deteriorates. Cartilage is a firm, slippery tissue that enables nearly frictionless joint motion. Eventually, if the cartilage wears down completely, bone will rub on bone.

It occurs when the protective cartilage that cushions the ends of your bones wears down over time.

Although osteoarthritis can damage any joint, the disorder most commonly affects joints in your hands, knees, hips and spine.

Osteoarthritis (OA) is the most common degenerative joint disease, affecting more than 25% of the population over 18 years-old. Pathological changes seen in OA joints include progressive loss and destruction of articular cartilage, thickening of the subchondral bone, formation of osteophytes, variable degrees of inflammation of the synovium, degeneration of ligaments and menisci of the knee and hypertrophy of the joint capsule (Loeser, Golgring *et al.,* 2012)

**Pathogenesis and Progression**

Osteoarthritis is traditionally thought of as a ‘wear and tear’ disease which occurs as we age. However, recent research suggests otherwise.

The pathogenesis of OA involves a degradation of cartilage and remodelling of bone due to an active response of chondrocytes in the articular cartilage and the inflammatory cells in the surrounding tissues.

The release of enzymes from these cells break down collagen and proteoglycans, destroying the articular cartilage. The exposure of the underlying subchondral bone results in sclerosis, followed by reactive remodelling changes that lead to the formation of osteophytes and subchondral bone cysts. The joint space is progressively lost over time.

Osteoarthritis (OA) results from an imbalance between breakdown and repair of the tissues in the synovial joints. Risk factors include trauma, overuse, obesity, and genetic predisposition. The etiopathogenesis of osteoarthritis has been divided into 3 stages.

In stage 1, proteolytic breakdown of the cartilage matrix occurs. Chondrocyte metabolism is affected, leading to an increased production of enzymes, which includes metalloproteinases (eg, collagenase, stromelysin) that destroy the cartilage matrix. Chondrocytes also produce protease inhibitors, including tissue inhibitors of metalloproteinases (TIMP) 1 and 2, but in amounts insufficient to counteract the proteolytic effect.

Stage 2 involves the fibrillation and erosion of the cartilage surface, with a subsequent release of proteoglycan and collagen fragments into the synovial fluid.

In stage 3, the breakdown products of cartilage induce a chronic inflammatory response in the synovium. Synovial macrophage production of metalloproteinases, as well as cytokines such as interleukin (IL) 1, tumor necrosis factor (TNF)-alpha, occurs. These can diffuse back into the cartilage and directly destroy tissue or stimulate chondrocytes to produce more metalloproteinases. Other proinflammatory molecules (eg, nitric oxide [NO], an inorganic free radical) may also be a factor in stage 3.

**The involvement of T and B Lymphocytes**

Activated T cells are known to enhance osteoclastogenesis and bone resorption. Because CD28 is expressed constitutively on T cells and its expression is down-regulated by chronic exposure to the inflammatory environment, we characterized co-stimulatory molecule expression on T cells from chronically infected patients. Cytofluorometric techniques are used to phenotypically characterize T cells, its co-stimulatory molecules and perforin secretion from infected and non-infected human bones. A higher T cell activation [human leucocyte antigen D-related (HLA-DR+)] is shown in infected compared to non-infected bones. Chronically infected human bones are characterized by an increase of CD28-negative CD4+ T cells, indicating long-term activated cells with cytotoxic ability. Therefore, this alteration of co-stimulatory molecules may modify interactions with osteoclasts and impact bone resorption.

B cells not only participate in proinflamatory reactions. They also play a role in regulation of immune responses. Regulatory B (Breg) cells are specific subsets that have an ability of immune response suppression. 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)

Breg cells are important in preventing the disease onset and also in sup-pressing the disease symptoms. Primarily, Breg cells are able to change T cell differentiation in behalf of a regulatory phenotype. It is considered that related interactions between Breg cells and T cells control the induction of T regulatory (Treg) cells and are important in maintaining Treg cell compartment recent findings, Breg cells have an ability to inhibit Th1immune responses by the production of IL-10 during chronic infections Furthermore, they are capable of indirect suppression of Th1 and Th17 cells differentiation by suppressing production of pro-inflammatory cytokines by dendritic cells.

In conclusion, bone tissue in humans appears to be a site of T cell activation and proliferation, the latter being decreased in chronic bacterial infections. Bone infections are associated with a high percentage of CD28− CD4 T cells exhibiting a cytotoxic phenotype as well as an up-regulated CD40/CD40L pathway on T cells. As activated T cells are already known to express RANKL, which is a crucial factor for osteoclastogenesis, our results suggest a creative line of work on the mechanisms of bone resorption in human BI. Moreover, we assume that biotherapies targeting co-stimulatory molecules might have significant but variable effects on bone resorption, depending on their membrane expression.

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