Discuss the involvement of T-and B-LYMPOCYTES IN THE PROGRESSION AND Pathogenesis of osteomyelitis and osteoarthritis

**NAME: ADEKANYE AYOTUNDE UTHMAN**

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**LECTURER: MR. EDEM E EDEM**

**Introduction to t- and b lymphocytes**

A lymphocyte is one of the subtypes of a white blood cell in a vertebrate's immune system. Lymphocytes include natural killer cells (which function in cell-mediated, cytotoxic innate immunity). Historically, immune responses have been classified as cellular or humoral. Cellular responses are mediated by T lymphocytes, which recognize and attack their targets directly or indirectly by enlisting the help of other immune cells, while humoral responses are characterized by the production of antibodies by B lymphocytes and their progeny, plasma cells. These antibodies permeate extracellular spaces, where they protect against infection and also contribute to tissue injury in autoimmunity and transplantation. B cells have therefore traditionally been associated with humoral immunity, but we now know that they are equally critical to cellular immunity. (Hoffman *et.,al* 2016).

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. Thus, humoral immunity depends on the B Cells while cell immunity depends on the T Cells. (Cano, R. L. E., & Lopera, H. D. E, 2013). T cells and B cells are the two types of lymphocytes that are involved in triggering the immune response in the body. Both T cells and B cells are produced in the bone marrow. The T cells migrate to the thymus for maturation. Both the T cells and B cells are involved in recognizing pathogens and other harmful, foreign materials inside the body such as bacteria, viruses, parasites and dead cells

**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 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 antigen-presenting cells APCs. (Rydzewska *et.,al 2018)*.

 T cells are a type of lymphocytes that develop in the thymus. They are also called T lymphocytes. These cells are primarily produced in the bone marrow and migrate to the thymus for maturation. The immature T cells differentiate into three types of T Cells: helper T cell, cytotoxic T cells, and suppressor T cells. The helper T cells primarily recognize antigens and activate both cytotoxic T cells and B cells. The B cells secrete antibodies and cytotoxic T cells destroy the infected cells by apoptosis. The suppressor T cells modulate the immune system in such a way to tolerate the self-antigens, preventing autoimmune diseases .Both helper and cytotoxic T cells recognize various antigens in the circulation system, which are shredded by pathogens. These antigens should be presented on the surfaces of the antigen presenting cell (APS). Macrophages,dendritic cells, Langerhans cells, and B cells are the types of APSs.

**B lymphocytes**

B cells develop from hematopoietic stem cells (HSCs) that originate from bone marrow which first differentiate into multipotent progenitor (MPP) cells, then common lymphoid progenitor (CLP) 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. B cells also play an immunomodulatory role in regulating the immune response by secreting cytokines that inhibit disease onset and/or progression (Hoffman et.,al 2016).

The discovery of B cells did not originate in the identification of a cell, but rather the identification of a protein (ie, Ig or antibody).The B-lymphocyte system is fully developed at birth. The origin of the human B lymphocyte is not well defined but fetal B lymphocytes can be recognized in the yolk sac, omentum, and fetal liver. After birth B-lymphocyte development takes place in the bone marrow.

**Introduction to Osteomyelitis**

Osteomyelitis is an infection and inflammation of the bone or the bone marrow. It is a devastating disease caused by microbial infection of bone.The most common causative species are the usually commensal staphylococci, with Staphylococcus aureus and Staphylococcus epidermidis responsible for the majority of cases. Staphylococcus aureus is responsible for the majority of chronic osteomyelitis cases and is often considered to be incurable due to bacterial persistence deep within bone.

The frequency of infection following elective orthopedic surgery is low, rates of reinfection are disturbingly high. (Bhowmik, D.,*et.al.,* 2018). It has traditionally been classified into three categories.

**The first category**, hematogenous osteomyelitis, is bone infection that has been seeded through the bloodstream.

**The second**, osteomyelitis due to spread from a contiguous focus of infection without vascular insufficiency, is seen most often after trauma or surgery, and is caused by bacteria which gain access to bone by direct inoculation (for example, a contaminated compound fracture) or extension to bone from adjacent contaminated soft tissue (for example, a prosthetic joint contaminated at the time of implantation).

**The third category**, osteomyelitis due to contiguous infection with vascular insufficiency, is seen almost exclusively in the lower extremities, most commonly as a diabetic foot infection ( Fritz, J. M., & McDonald, J. R. (2008).

Osteomyelitis is an inflammatory bone disease that is caused by an infecting microorganism and leads to progressive bone destruction and loss.

Treatment often involves both antimicrobials and surgery. In those with poor blood flow, amputation may be required. The 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)

 **Involvement of T and B Lymphocytes in Osteomyelitis**

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.

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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)

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).

**Introduction to 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.

Osteoarthritis is the most common form of arthritis, affecting millions of people worldwide.

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.

**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 breaks 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.

 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, the results suggest a creative line of work on the mechanisms of bone resorption in human BI. Moreover, biotherapies assume targeting co-stimulatory molecules might have significant but variable effects on bone resorption, depending on their membrane expression.

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