Name:Jeje Susan Pius
Matric number:16/mhs03/015
Department: HUMAN ANATOMY
Course Title: INTRODUCTION TO HISTOPATHOLOGY
Course Code: ANA 404

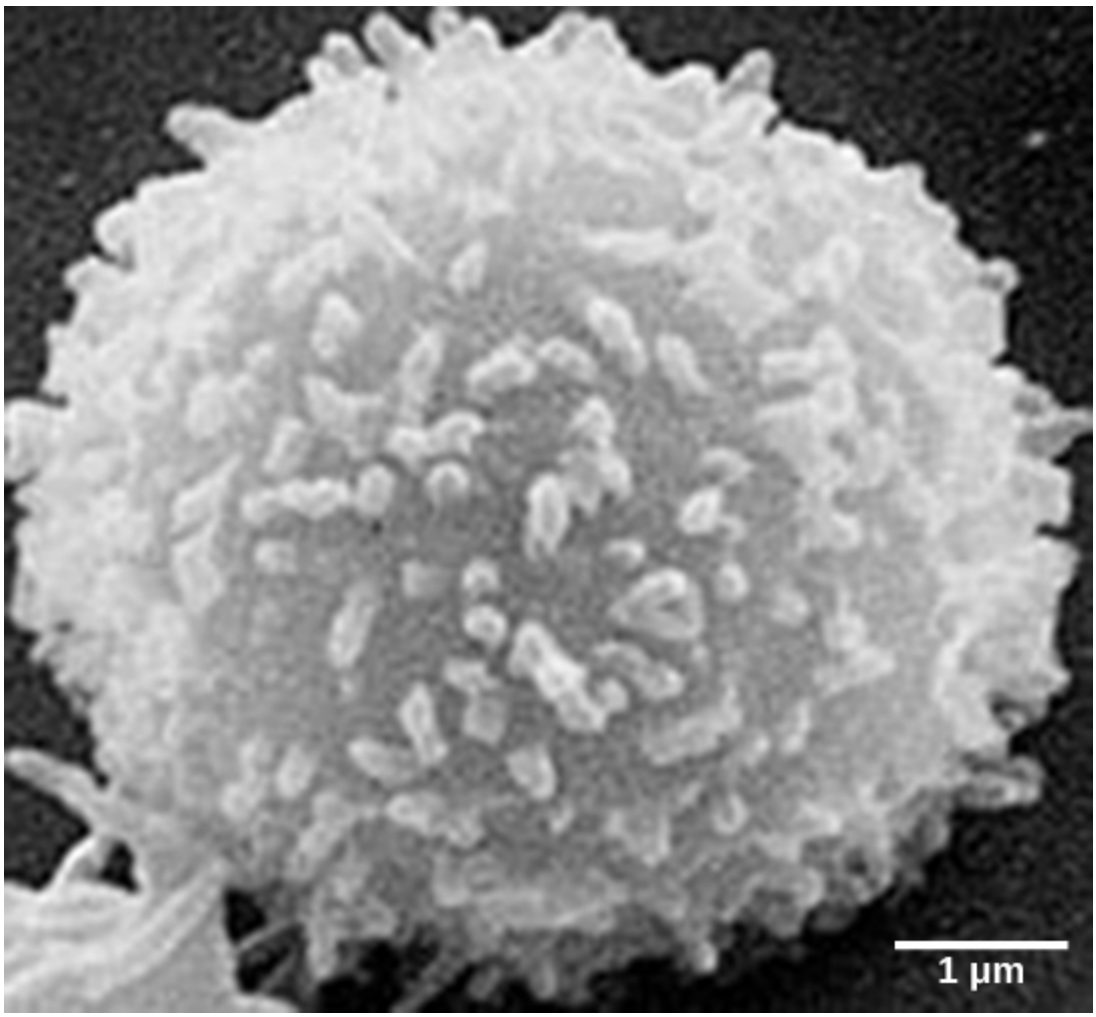
Question

Discuss the involvement of T– and B–lymphocytes in the pathogenesis and progression of osteomyelitis and osteoarthritis.

The bone marrow is extremely important to the immune system because all the body's blood cells (including T and B lymphocytes) originate in the bone marrow. B lymphocytes remain in the marrow

T cells (thymus cells) and B cells (bone marrow- or bursa-derived cells[a]) are the major cellular components of the adaptive immune response. T cells are involved in cell-mediated immunity, whereas B cells are primarily responsible for humoral immunity(relating to antibodies). The function of T cells and B cells is to recognize specific "non-self" antigens, during a process known as antigen presentation. Once they have identified an invader, the cells generate specific responses that are tailored maximally to eliminate specific pathogens or pathogen-infected cells. B cells respond to pathogens by producing large quantities of antibodies which then neutralize foreign

objects like bacteria and viruses. In response to pathogens some T cells, called *T helper cells*, produce cytokines that direct the immune response, while other T cells, called cytotoxic T cells, produce toxic granules that contain powerful enzymes which induce the death of pathogen-infected cells. Following activation, B cells and T cells leave a lasting legacy of the antigens they have encountered, in the form of memory cells. Throughout the lifetime of an animal, these memory cells will "remember" each specific pathogen encountered, and are able to mount a strong and rapid response if the same pathogen is detected again; this is known as acquired immunity.



This scanning electron micrograph shows a T lymphocyte, which is responsible for the cell-mediated immune response. T cells are able to recognize antigens. (credit: modification of work by NCI; scale-bar data from Matt Russell)

T lymphocytes

T cells encompass a heterogeneous population of cells with extremely diverse functions. Some T cells respond to APCs of the innate immune system, and indirectly induce immune responses by releasing cytokines. Other T cells stimulate B cells to prepare their own response. Another population of T cells detects APC signals and directly kills the infected cells. Other T cells are involved in suppressing inappropriate immune reactions to harmless or "self" antigens.

T and B cells exhibit a common theme of recognition/binding of specific antigens via a complementary receptor, followed by activation and self-amplification/maturation to specifically bind to the particular antigen of the infecting pathogen. T and B lymphocytes are also similar in that each cell only expresses one type of antigen receptor. Any individual may possess a population of T and B cells that together express a near limitless variety of antigen receptors that are capable of recognizing virtually any infecting pathogen. T and B cells are activated when they recognize small components of antigens, called **epitopes**, presented by APCs, illustrated in below

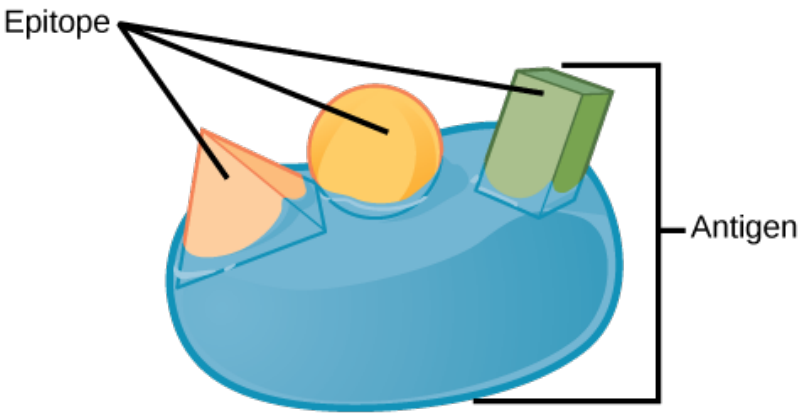


Figure 2. An antigen is a macromolecule that reacts with components of the immune system. A given antigen may contain several motifs that are recognized by immune cells. Each motif is an epitope. In this figure, the entire structure is an antigen, and the orange, salmon and green components projecting from it represent potential epitopes.

the recognition occurs at a specific epitope rather than on the entire antigen; for this reason, epitopes are known as “antigenic determinants.” In the absence of information from APCs, T and B cells remain inactive, or naïve, and are unable to prepare an immune response. The requirement for information from the APCs of innate immunity to trigger B cell or T cell activation illustrates the essential nature of the innate immune response to the functioning of the entire immune system.

Naïve T cells can express one of two different molecules, CD4 or CD8, on their surface, and are accordingly classified as $CD4^+$ or $CD8^+$ cells. These molecules are important because they regulate how a T cell will interact with and respond to an APC.

Naïve $CD4^+$ cells bind APCs via their antigen-embedded MHC II molecules and are stimulated to become **helper T (T_H) lymphocytes**, cells that go on to stimulate B cells (or cytotoxic T cells) directly or secrete cytokines to inform more and various target cells about the pathogenic threat. In contrast, $CD8^+$ cells engage antigen-embedded MHC I molecules on APCs and are stimulated to become **cytotoxic T lymphocytes (CTLs)**, which directly kill infected cells by apoptosis and emit cytokines to amplify the immune response. The two populations of T cells have different mechanisms of immune protection, but both bind MHC molecules via their antigen receptors called T cell receptors (TCRs). The CD4 or CD8 surface molecules differentiate whether the TCR will engage an MHC II or an MHC I molecule. Because they assist in binding specificity, the CD4 and CD8 molecules are described as coreceptors.

T lymphocytes originate from precursor stem cells in
fetal liver and bone marrow and differentiate into mature cell types after migration to the thymus (Young, Q,2010) . T lymphocytes may be categorized based on their distinct function into cytotoxic T lymphocytes (expressing the surface protein cluster of differentation (CD) 8 and responsible mainly for immune defence against intracellular pathogens and for tumour surveillance) and helper T lymphocytes (expressing the surface protein CD4 expressed on the professional antigen-presenting cells (APCs) surface. Both are necessary for production of an
adequate immune response (Romangnani,s,2006). T cells have on their surface T cell antigen receptors (TCR) responsible for recognition of an antigen/major histocompatibility complex (HLA complex), immunological accessory molecule

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 [Kondom,M,2010)]. B cells represent mainly the humoral immunity. Nevertheless, their role as a cell itself is equally relevant.

osteoarthritis (OA) is regarded as a prevalent cause of morbidity and disability worldwide. OA shows many disease characteristics, such as cartilage degradation, moderate synovial inflammation, pain, alteration of bony structure, and impaired mobility. However, despite the severity of the disease, relatively little is known about its exact etiology. Recent compelling investigations have attributed the onset of OA to various person-level factors such as age, sex, obesity, and diet and joint-level factors such as injury, malalignment, and abnormal joint loading. Although more and more researchers have recently presented hypotheses concerning the involvement of these factors in OA, especially for person-level factors, few of their hypotheses have been demonstrated experimentally, and some have even been challenged by the latest observational studies and clinical trials.

Of the several factors potentially involved in the pathogenesis of OA, T cell-mediated immune responses and their influence . The scientific community once understood

OA to be induced by mechanical stress in the form of cartilage destruction, with minimal if any involvement of immune responses. Thus, OA was regarded as a non-inflammatory disease, in contrast with rheumatoid arthritis (RA), an inflammatory disease. little difference has been found in the percentages of T cells, B cells, and natural killer cells in the peripheral blood between patients with OA and RA (.Leheita et al) reflected on the similarity of the immune cell profiles of RA and OA and suggested that abnormalities in T cells may also contribute to the pathogenesis of OA. Further experiments indicated that inflammation in OA is anatomically restricted and varies in intensity. The synovial membranes in regions rimming the cartilage of OA patients, which contain T cells bordered by B lymphocytes and plasma cells, showed a pronounced inflammatory response. In contrast, only a few infiltrating lymphocytes were observed in the synovial membranes taken from macroscopically non-inflamed areas in OA patients. This may explain the suggestion made by some researchers that immune responses are not involved in the pathogenesis of OA. When synovial samples from patients with knee OA were analyzed, the synovial lining cells showed strong immunoreactivity and phagocytic potential with cluster of differentiation (CD) 68 antibodies .

To date, various immune cells have been identified in the synovial membranes of OA patients, such as macrophages, T cells, mast cells, B cells, plasma cells, natural killer cells, dendritic cells, and granulocytes. abundantly infiltrate the synovial tissues of OA patients. For example, macrophages represent approximately 65% of the immune

cells that infiltrate the synovial tissues of patients with OA, and T cells make up 22% of the infiltrate .

Osteomyelitis

infection of the bone and/or bone marrow. The pathogenesis of these diseases can follow

acute, subacute or chronic courses and involves a range of contributory host and pathogen factors. and a variety of antimicrobials with different spectrums

of activity against specific pathogens have been developed. Also, new operative techniques, such as fixation and muscle flaps, and innovative delivery systems for antibiotics have been added to our arsenal. In spite of these advances, however, osteomyelitis remains difficult to treat, with considerable morbidity and costs.

Osteomyelitis can be classified by duration (acute or

chronic), pathogenesis (trauma, contiguous spread, hematogenous, surgical), site, extent, or type of patient.

Although several classifications of osteomyelitis have

been described by different authors, the two most widely

used in the medical literature and in clinical practice are

the classification systems by Waldvogel et al.1 and

Cierny et al.2 Under the Waldvogel system, osteomyelitis is first described according to duration, either acute

or chronic. Second, the disease is classified according to source of infection, as

hematogenous when it originates from a bacteremia or as contiguous focus when it originates from an infection in a nearby tissue. A final category of the classification is vascular insufficiency. One of the limitations of the Waldvogel classification system is that it does not consider infection originating from direct penetration of microorganisms.

development of osteomyelitis (Conrad, 2010). The pathogenesis of this process has been

theoretically described. Inoculation of the metaphyseal vessels occurs at the transition point from the arteriolar vessels to the venous sinusoids, slowing blood flow and increasing vascular turbulence (Jansson et al., 2009). These sites of turbulence may be predisposed to bacterial infection by providing an opportunity for local invasion

Although rarely seen in developed countries, haematogenous osteomyelitis may take on a chronic course within bone if left untreated. Sequelae of this devastating condition may include chronic sinuses with exposed bone, loss of structural integrity and growth disturbances (Beckles et al., 2010).

Local trauma to bone in the setting of bacteraemia may also be a contributing factor. rates of haematogenous osteomyelitis when

direct injury to bone was combined with intravenous bacterial seeding. (Kabak et al., 1999;

Morrissy & Haynes, 1989). A recent series of 450 cases of acute haematogenous osteomyelitis

found the rate of preceding blunt trauma to be 63% (Labbe et al., 2010). Further

research is needed to elucidate the role of trauma in this condition.

Aetiology of osteomyelitis

The spectrum of agents associated with osteomyelitis is an ever-widening one, partly because of accumulating evidence to suggest that microorganisms previously considered as specimen contaminants are capable of causing infection (Haidar et al., 2010; Wong et al., 2010) and partly because of the increasing application of newer diagnostic modalities, such as DNA amplification. These methodologies are more sensitive than conventional microbiological techniques in identifying conventional, emerging and new pathogens in clinical material (Bang et al., 2008; Ceroni et al., 2010; Cremniter et al., 2008). Although Staphylococcus aureus remains the pre-eminent cause of infection, the wide and increasing range of aetiological agents associated with osteomyelitis presents a challenge to the

clinician in terms of selection of empiric antimicrobial therapy; nevertheless particular clinical features as well as patient-specific risk factors and underlying conditions can be used to guide treatment.

spread from a contiguous site or following haematogenous seeding. The latter is more likely to be associated with monomicrobial infection while the former is often polymicrobial in origin including obligately anaerobic bacteria Osteomyelitis in individuals with vascular insufficiency including patients with diabetes mellitus is also frequently polymicrobial (Powlson & Coll, 2010).

There are also aetiological associations with patient age. In neonates, for example, the bacteria most frequently associated with acute haematogenous osteomyelitis are those

which cause neonatal sepsis, notably Lancefield group B streptococci (Streptococcus agalactiae) and Escherichia coli as well as S. aureus (Dessi et al., 2008). In older children, S. aureus infection predominates and in some countries, such as the US, community-acquired methicillin-resistant strains (CA-MRSA) are increasingly recognized (Vander Have et al., 2009). Kingella kingae has also emerged in recent years as an important cause of osteomyelitis in children (Dubnov-Raz et al., 2008). In contrast, Haemophilus influenzae infections, once common in patients aged under five years, have markedly declined as a result of vaccination against Pittman type b strains of this bacterium (Howard et al., 1999). In adults, as with younger patients, S. aureus is the most frequent agent of infection.

References

1-Adams, C. S., Antoci, V., Jr., Harrison, G., Patal, P., Freeman, T. A., Shapiro, I. M., et al. (2009). Controlled release of vancomycin from thin sol-gel films on implant surfaces successfully controls osteomyelitis. Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society, Vol. 27, No. 6, pp. (701-709)

2-Ahmed, S., Meghji, S., Williams, R. J., Henderson, B., Brock, J. H., & Nair, S. P. (2001). Staphylococcus aureus fibronectin binding proteins are essential for internalization by osteoblasts but do not account for differences in intracellular levels of bacteria. Infect Immun, Vol. 69, No. 5, pp. (2872-2877), 0019-9567

3-Akiyama, H., Torigoe, R., & Arata, J. (1993). Interaction of Staphylococcus aureus cells and silk threads in vitro and in mouse skin. J Dermatol Sci, Vol. 6, No. 3, pp. (247-257), 0923-1811

4-Al-Ola, K., Mahdi, N., Al-Subaie, A. M., Ali, M. E., Al-Absi, I. K., & Almawi, W. Y. (2008). Evidence for HLA class II susceptible and protective haplotypes for osteomyelitis in pediatric patients with sickle cell anemia. Tissue Antigens, Vol. 71, No. 5, pp. (453-457),

5-Alexander, E. H., Rivera, F. A., Marriott, I., Anguita, J., Bost, K. L., & Hudson, M. C. (2003). Staphylococcus aureus - induced tumor necrosis factor - related apoptosis - inducing ligand expression mediates apoptosis and caspase-8 activation in infected osteoblasts. BMC Microbiol, Vol. 3, No., pp. (5), 1471-2180

6-Arens, S., Schlegel, U., Printzen, G., Ziegler, W. J., Perren, S. M., & Hansis, M. (1996).

Influence of materials for fixation implants on local infection. An experimental study of steel versus titanium DCP in rabbits. J Bone Joint Surg Br, Vol. 78, No. 4, pp. (647-651), 0301-620X

7-Asensi, V., Alvarez, V., Valle, E., Meana, A., Fierer, J., Coto, E., et al. (2003). IL-1 alpha (-889) promoter polymorphism is a risk factor for osteomyelitis. American Journal of Medical Genetics. Part A, Vol. 119A, No. 2, pp. (132-136)

8-Asensi, V., Montes, A. H., Valle, E., Ocaña, M. G., Astudillo, A., Alvarez, V., et al. (2007). The NOS3 (27-bp repeat, intron 4) polymorphism is associated with susceptibility to osteomyelitis. Nitric Oxide: Biology and Chemistry / Official Journal of the Nitric Oxide Society, Vol. 16, No. 1, pp. (44-53)

9-Baier, R. E., Meyer, A. E., Natiella, J. R., Natiella, R. R., & Carter, J. M. (1984). Surface properties determine bioadhesive outcomes: methods and results. J Biomed Mater Res, Vol. 18, No. 4, pp. (327-355), 0021-9304

10-Balaban, N., Cirioni, O., Giacometti, A., Ghiselli, R., Braunstein, J. B., Silvestri, C., et al. (2007). Treatment of Staphylococcus aureus biofilm infection by the quorum?sensing inhibitor RIP. Antimicrob Agents Chemother, Vol. 51, No. 6, pp. (2226-2229), 0066-4804

11-Bang, D., Herlin, T., Stegger, M., Andersen, A. B., Torkko, P., Tortoli, E., et al. (2008). Mycobacterium arosiense sp. nov., a slowly growing, scotochromogenic species causing osteomyelitis in an immunocompromised child. Int J Syst Evol Microbiol, Vol. 58, No. Pt 10, pp. (2398-2402), 1466-502

12- Yang Q, Jeremiah Bell J, Bhandoola A. T-cell lineage determination. ImmunolRev. 2010;238:

13 . Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes.

Nature. 1996;383:787–93.

14 . Romagnani S. Regulation of the T cell response. Clin Exp Allergy. 2006;36:

1357–66.

15 . Kronenberg M, Siu G, Hood LE, Shastri N. The molecular genetics of the Tcell antigen receptor and T- cell antigen recognition. Annu Rev Immunol.

1986;4:529–91.

16- Isakov N. Cell activation and signal initiation. Immunol Today. 1988;9:251–2.

17-. Ochs HD, Oukka M, Torgerson TR. TH17 cells and regulatory T cells in primary

immunodeficiency diseases. J Allergy Clin Immunol. 2009;123:977–83.

18. Jager A, Kuchroo VK. Effector and regulatory T-cell subsets in autoimmunity

and tissue inflammation. Scand J Immunol. 2010;72:173–84.

19. Mosmann TR, Coffman RL. Th1 and Th2 cells: different patterns of lymphokine

secretion lead to different functional properties. Ann Rev Immunol. 1989;7:145–73.

20. Hu C, Salgame P. Inability of interleukin-12 to modulate T-helper 0 effectors

to T-helper 1 effectors: a possible distinct subset of T cells. Immunology.

1999;97:84–91.

21. Parijs LV, Abbas AK. Homeostasis and self-tolerance in the immune system:

turning lymphocytes off. Science. 1998;280:243–8.

22- Bartalena L, Tanda ML, Piantanida A, et al. Environment and thyroid autoimmunity.

In: Wiersinga WM, Drexhage HA, Weetman AP, et al., editors. The thyroid and

autoimmunity. Stuttgart: Verlag; 2007. p. 60–73.

23- Tamai H, Ohsako N, Takeno K, et al. Changes in thyroid function in euthyroid subjects with family history of graves' disease; a follow up study of 69 patients. J Clin Endocrinol Metab. 1980;51:1123–8.

24 . Kraiem Z, Baron E, Kahana L, Sadeh O, Sheinfeld M. Changes in stimulating and blocking TSH receptor antibodies in a patient undergoing three cycles of transition from hypo to hyper-thyroidism and back to hypothyroidism. Clin Endocrinol. 1992;36:211.

25- Ajjan RA, Watson PF, Weetman AP. Cytokines and thyroid function. Adv Neuroimmunol. 1996;6:359–86.

26. Ben-Skowronek I, Szewczyk L, Kulik-Rechberger B, Korobowicz E. The differences in T and B cell subsets in thyroid of children with graves' disease and Hashimoto's thyroiditis. World J Pediatr. 2013;9:245–50.