|  |
| --- |
|  |

|  |
| --- |
| **THE INVOLVEMENT OF T- AND B-LYMPHOCYTES IN THE PATHOGENESIS AND PROGRESSION OF OSTEOMYELITIS AND OSTEOARTHRITIS** |
| ASSIGNMENT |
|  |
| ANA404 – INTRODUCTION TO HISTOPATHOLOGY |
| OSAMOR MICHELLE |
| **16/MHS01/213** |
| **4/21/2020** |
|  |

INVOLVEMENT OF T- AND B-LYMPHOCYTES IN PATHOGENESIS 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 vertebrae (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.

A commonly used aetiological classification distinguishes between three types of osteomyelitis: acute or chronic haematogenous disease seeded by organisms in the bloodstream, local spread from a contiguous source of infection and secondary osteomyelitis related to vascular insufficiency.

Acute haematogenous osteomyelitis

Acute haematogenous osteomyelitis refers to infection of bone resulting from bacteria in the bloodstream. This is seen most often in children, with initial infection thought to occur in the richly vascularised metaphyseal region (Gutierrez, 2005). Children are thought to experience frequent episodes of bacteraemia, often with no apparent symptoms, leading to seeding and 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).

Vertebral osteomyelitis

Osteomyelitis involving the spine is also most commonly caused by haematogenous seeding of bacteria into the vertebrae (Tay *et al*., 2002). The pathophysiology of this condition reflects the unique vascular structures of the spine. The venous anatomy of the spine, originally investigated for its role in cancer metastasis, allows retrograde flow from the pelvic venous plexus due a lack of valvular structures, providing an opportunity for haematogenous deposition of bacteria (Batson, 1967). Fine arteriolar structures surrounding the vertebral end plate may also represent a location at which bacteria can become trapped (Wiley & Trueta, 1959).

Osteomyelitis secondary to contiguous infection

In adult patients, the majority of osteomyelitis cases are due to inoculation from contiguous infection. Sources can include direct contamination at a site of injury, iatrogenic contamination at the time of an invasive procedure, or invasive infection from surrounding soft tissue. The epidemiology of contiguous infection osteomyelitis is biphasic, with young patients suffering trauma and related surgery and older patients suffering decubitus ulcers

Host factors

The pathogenesis of osteomyelitis is a complex process involving interactions between a host and an infectious agent. The host’s inflammatory response to a pathogen can further the physical spread of disease by clearing space in bone. Predisposing genetic differences in immune function are increasingly seen as an aetiological factor in some cases of osteomyelitis. Acquired factors such as diseases causing immune or vascular compromise and implantation of foreign materials are frequently involved in the disease process as well.

Pathogen factors

The initial event in the localization of infection appears to be adhesion of the bacteria to the extracellular matrix (ECM). Various factors govern this adhesion process. Once a bacteria reaches the biomaterial surface by haematogenous route they acquire a conditioning film of ECM proteins. Osteoblast play an active role in the internalization of the bacteria. Subsequently a multi-layered biofilm is made by the bacteria, which protects it from phagoctytosis and antibiotics.

Chronic bone infection is associated with bone resorption. From animal studies, CD3/CD28-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, it was characterized that co-stimulatory molecule expression on T cells from chronically infected patients. cytoﬂuorometric techniques was used to phenotypically characterize T cells, its co-stimulatory molecules and perforin secretion from infected and noninfected human bones. Chronic bone infection was deﬁned as infection lasting for more than a month. A higher T cell activation [human leucocyte antigen D-related (HLA-DR+)] in infected was shown compared to noninfected bones: median being 16 versus 7%,P = 0·009 for CD4 T cells,and 33 versus 15%, P = 0·038 for CD8 T cells, respectively. However, T cell proliferation (Ki67+) was lower for CD8 T cells in infected bones: 26 versus 34%, P = 0·045. In contrast, we detected no difference in apoptosis and regulatory T cells. In infected bone, it was found that higher CD28-negative CD4+ T cells compared to non-infected bone: 20 versus 8%,respectively (P = 0·005); this T cell subset had higher CD11b expression and perforin secretion. Chronically infected human bones are characterized by an increase of CD28-negative CD4+ T cells, indicating long-term activated cells with cytotoxic ability. Therefore, the alteration of co-stimulatory molecules showed to modify interactions with osteoclasts and impact bone resorption.

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

osteoarthritis is a degenerative joint disease whose prevalence increases with age, and includes a group of pathologies involving structural degeneration of the joint resulting in pain and disability. Treatment is currently limited to the management of pain, exercise and lifestyle modification, and ultimately joint replacement surgery. There is evidence of osteoarthritis in all individuals over the age of 60 but symptomatic osteoarthritis, (disease that requires medical treatment), occurs in only 15%. The reasons why osteoarthritis only becomes symptomatic in some people remain unexplained.

Recent magnetic resonance imaging studies have highlighted a very high frequency of pathology involving cartilage, bone and synovium (soft tissue lining of the joints), with relevance in structure-pain associations. Inflammation of the synovium (synovitis) is a well-recognised feature of osteoarthritis, notably with an important role for interleukin-1beta (IL-1β). Many of the age-related defects of the immune system highlighted above are involved in the pathogenesis of osteoarthritis. Furthermore, mechanical forces which produce cartilage damage breakdown products have been proposed as a source of immune stimulation, promoting persistent low-grade inflammation. Antigen-driven stimuli using collagen breakdown products as neo-antigens were suggested to lead to specific T/B-cell responses. Innate immune responses to calcium crystal deposition were shown to initiate IL-1β production.

A hypothesis was made as it was discovered that the interactions between the musculoskeletal and the immune system are important sources of divergence between healthy people and patients with osteoarthritis. They can be used to better understand the pathology of osteoarthritis by distinguishing ageing specific changes from those that are osteoarthritis specific. It was shown that the immune cell composition of the blood of osteoarthritis patients is quite different from that of aged-matched controls notably with major changes in CD4/CD8 T-cells, loss of regulatory T-cells and alteration in the T to B-cell ratio. Synovitis has been proposed as niche for B-cell maturation and the production of auto-antibodies in osteoarthritis. However, B-cell infiltration in osteoarthritis is quite independent of T-cells and the presence of germinal centre like structures is rarely observed.

It was proposed and investigated that mechanism of auto-reactive B-cell development in osteoarthritis under the hypothesis that it is T-cell independent and uses alternative maturation signals brought in by the innate immune system. The IgM repertoire is quite broadly developed (targeting many auto-antigens in health even at a younger age), however maturation of IgG is achieved with the help of T-cells. In ageing (and osteoarthritis) T-cell help is defective and alternative signals can be used to mature B-cells. These include signals from the innate immune system, such as those provided by the activation of TLR on B-cells which result in the expression of the XBP-1 transcription factor, an essential regulator of B-cell maturation.

The events leading to B-cell maturation and isotype switching are known and steps are reproducible in vitro. B-cell cultures were used to establish the role of TLR activation on B-cell maturation and effect on the activation of XBP-1. Gene expression profiling addressed the pathways implicated in the alternative maturation process including XBP-1 and genes of the B-cell receptor and immunoglobulin rearrangement pathways. These profiles were compared to those obtained from B-cell cultures stimulated with T-cell help signals (CD40::CD40L). Selected genes will then be tested in B-cells purified from the blood from healthy controls and osteoarthritis patients and from osteoarthritis synovial tissue to assess the mean by which B-cells mature and produce IgGs (i.e. T-cell dependent or independent pathways).

The main use of measuring T and B lymphocytes response is in establishing the correct diagnosis between suspected osteomyelitis and other bone tumours.

Other ways in which t-lymphocytes are involved in osteoarthritis pathogenesis are:

T cells infiltrating the synovial membrane of patients with OA express early, intermediate, and late activation antigens

References

F Ponchel, AN Burska, EA Hensor R Raja, M Campbell, P Emery, PG Conaghan. Changes in peripheral blood immune cell composition in osteoarthritis. Osteoarthritis and Cartilage, in press, doi: 10.1016/j.joca.2015.06.018

SAVIC S, L OUBOUSSAD, LJ. DICKIE, J GEILER, C WONG, GM. DOODY, SM. CHURCHMAN, F PONCHEL, P EMERY, GP. COOK, MH. BUCH, RM. TOOZE, MF. MCDERMOTT. TLR dependent XBP-1 activation induces an autocrine loop in rheumatoid arthritis synoviocytes. Journal of autoimmunity 2013, 50:59–66.

Beronius M, Bergman B, Anderson R. Vertebral osteomyelitis in Goteborg, Sweden: a retrospective study of patients during 1990–95. Scand J Infect Dis 2001;33:527–532

Dahl LB, Hoyland AL, Dramsdahl H, Kaaresen PI. Acute osteomyelitis in children: a population-based retrospective study 1965 to 1994. Scand J Infect Dis 1998;30:573–577

Trobs R, Moritz R, Buhligen U, et al. Changing pattern of osteomyelitis in infants and children. Pediatr Surg Int 1999; 15:363–372

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)

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

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

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. (453457),

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

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

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)

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)

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

Waldvogel FA, Medoff G, Swartz MN. Osteomyelitis—a review of clinical features, therapeutic considerations and unusual aspects. 3: osteomyelitis associated with vascular insufﬁciency. N Engl J Med 1970;282:316–322

Cierny G III, Mader JT, Penninck JJ. A clinical staging system for adult osteomyelitis. Clin Orthop Relat Res 2003; 414:7–24

Lew DP, Waldvogel FA. Osteomyelitis. N Engl J Med 1997; 336:999–1007

Song KM, Sloboda JF. Acute hematogenous osteomyelitis in children. J Am Acad Orthop Surg 2001;9:166–175

Nasser S. The incidence of sepsis after total hip replacement arthroplasty. Semin Arthroplasty 1994; 5:153–59. 2 Lew DP, Waldvogel FA. Osteomyelitis. N Engl J Med 1997; 363:999–1007.