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An Assignment On

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

BY

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INTRODUCTION

The term osteomyelitis encompasses a broad group of infectious diseases characterized by 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. A commonly used etiological classification distinguishes between three types of osteomyelitis: acute or chronic hematogenous disease seeded by organisms in the bloodstream, local spread from a contiguous source of infection and secondary related to vascular insufficiency (Roy *et al.,* 2012).

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). 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.

Osteoarthritis result from failure of chondrocytes to maintain homeostasis between synthesis and degradation of these extracellular matrix components (Heijink *et al*., 2012). It is not known what initiates the imbalance between the degradation and the repair of cartilage. Trauma causing a microfracture or inflammation causing a slight increase in enzymatic activity may allow the formation of ‘wear’ particles, which could be then engulfed by resident macrophages (Wang *et al*., 2013). At some point in time, the production of these ‘wear’ particles overwhelms the ability of the system to eliminate them and they become mediators of inflammation, stimulating the chondrocyte to release degradative enzymes.

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 (Yang *et al*., 2010). T lymphocytes may be categorized based on their distinct function into cytotoxic T lymphocytes (expressing the surface protein cluster of differentiation (CD) 8 and responsible mainly for immune defense against intracellular pathogens and for tumor surveillance) and helper T lymphocytes (expressing the surface protein CD4) (Abbas and Murphy, 1996). In this review, we focus on CD 4+ cells. Helper T cells (naïve CD4+ T lymphocytes) are triggered when they are presented with peptide antigens by MHC (major histocompatibility complex) class II molecules, which are expressed on the professional antigen-presenting cells (APCs) surface. Both are necessary for production of an adequate immune response (Romagnani, 2006).

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 (Kondo, 2010). B cells represent mainly the humoral immunity. Nevertheless, their role as a cell itself is equally relevant. In practise, they are activated in patients with AITD (Pyzik *et al*., 2015). In Graves’ Disease, B cells play a vital role as they are the source of pathognomonic activating autoantibodies (TRAb) against thyroid-stimulating hormone receptor (TSHR) (Ramos and Marazuela, 2016). TRAb, by binding to the receptor, chronically stimulates it. TSHR is expressed on thyroid follicular cells; thus, the consequence of this chronic stimulation is an increased production and secretion of thyroid hormones T4 and T3 (Ajjan *et al*., 1996). Although the role of B cells in development of Hashimoto’s thyroiditis is not as significant as in GD, it should be mentioned that they produce autoantibodies to the thyroglobulin (Tg) and thyroid peroxidase (TPO), which are thyroid self-antigens. Antibody-dependent cell-mediated cytotoxicity is a meaningful factor responsible for apoptosis of thyroid follicular cells in HT.

B cells can also serve as APCs. They have a transmembrane receptor, called BCR (a surface immunoglobulin), which enables them to identify specific antigens, against which they initiate an immune response and synthesize antibodies, and present fragments of these antigens to CD4+ T cells using MHC class II molecules (Kambayashi and Laufer, 2016). When the antigen is uncommon, B cells may be the dominant APCs as they have an ability of up concentration antigens on the cell due to the presence of BCR in the cell membrane (Kristensen, 2016). T helper (Th) cells reciprocally support activation of B cells. Particular attention was paid to sequencing of thyroid antibodies and defining B cell epitopes in TSH receptor. This, in turn, could enable further understanding of the pathogenesis of GD, which is a cause of triggering TSHR leading to development of this disease (Nagayama, 2007). However, the pace of the autoimmune reaction in AITD is usually slow, which leads its proliferation and differentiation involving many different polyclonal B and T cells.

Role of T-lymphocytes in the Pathogenesis of Osteoarthritis.

Pelletier et al cited macrophages as the exclusive source of inflammation in osteoarthritis. However, the role of T cells in the inflammatory process has not been considered. T cell infiltrates are frequently detected in the synovial membrane (SM) of patients with OA (Sakkas *et al*., 1998). These infiltrates are often angiocentric and are associated with activation of local vascular endothelial cells, as suggested by the increase in expression of E-selectin (Koch, 1993). In patients with advanced OA, T cell infiltrates in the SM exhibit a nodular pattern in 37% to 65% of the patients and express early (CD69), intermediate (CD25), and late (CD45RO, HLA–DR) activation antigens. Additionally, T cell cytokine transcripts of the Th1 type interferon- (IFN) and interleukin-2 (IL-2) and IL-10 were found in the SM of patients with OA, whereas IL-4 and IL-5 were not detected. There were no statistical differences in the levels of IFN and IL-2 transcripts in the SM between patients with rheumatoid arthritis (RA) and OA, when normalized for T cell number equivalents. However, when the levels of IFN transcripts were normalized for total cell number equivalents, they were lower in OA than in RA. The presence of substantial proportions of T cells expressing early, intermediate, and late activation antigens and of the Th1 cytokine pattern in chronic SM lesions of patients with OA strongly suggests that T cells at least contribute to chronic inflammation in these patients. This Th1 response may be driven by macrophages.

Macrophages and synovial lining cells express IL-12, a cytokine that drives the Th1 immune response. OA synovial fluid exhibits increased levels of macrophage inflammatory protein, a ligand for the chemokine receptor CCR5, present on Th1 cells (Loetscher *et al*., 1998). Although these findings may be explained by a nonspecific activation of T cells, we have demonstrated (Scanzello *et al*., 1999) the presence of oligoclonal populations of T cells in the SM of 4 out of 5 patients with advanced OA. Amplification ofchain T cell receptor (TCR) transcripts from the SM of patients with OA by either nonpalindromic adaptor polymerase chain reaction (PCR) or V-specific PCR, followed by cloning and sequencing of the amplified transcripts, revealed substantial proportions of identical-chain TCR transcripts, suggesting the presence of oligoclonal populations of T cells. These results strongly suggest that T cells have undergone antigen-driven proliferation and clonal expansion in situ in the SM of patients with OA, in response to as-yet-unidentified antigens. These antigen(s) are not known, but one study suggested a self-reactive immune response to chondrocyte membrane components (Alsalameh *et al*., 1990). Like other conditions of chronic T cell activation, such as RA, systemic lupus erythematosus, and tumor-infiltrating lymphocytes (Finke *et al*., 1993) T cells in the SM of patients with OA show decreased expression of CD3-chain transcripts and protein. The inflammation in OA may not be confined within the joints. One study described perivascular lymphocytic infiltrates in muscle biopsies of 18% of patients with OA (Voskuyl *et al*., 1998). Activated T cells, through cell contact– dependent interaction or through soluble mediators, can stimulate monocytes to produce cytokines. In rheumatoid synovitis, T cells were found to be largely responsible for the production of metalloproteinase. All these results taken together strongly suggest that a T cell immune response occurs in OA. Substantial evidence has been accumulated suggesting that OA is an inflammatory disease. The traditional view that OA is a noninflammatory disease must be revised. We believe that it is difficult to explain the chronic inflammation that is observed in the SM of patients with OA without a role for T cells and a role for putative antigen(s) in the initiation and propagation of the disease.

REFERENCES

Mayank Roy, Jeremy S. Somerson, Kevin G. Kerr and Jonathan L. Conroy (2012). Pathophysiology and Pathogenesis of Osteomyelitis, Osteomyelitis, Prof. Mauricio S Baptista (Ed).

Heijink A, Gomoll AH, Madry H. Biomechanical considerations in the pathogenesis of osteoarthritis of the knee, Knee Surgery, Sports Traumatology, Arthroscopy. 2012; 20:423–435.

Wang M, Peng Z, Vasiliev K. Investigation of wear particles generated in human knee joints using atomic force microscopy. Tribology Letters. 2013; 51:161–170.

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.

Yang Q, Jeremiah Bell J, Bhandoola A. T-cell lineage determination. Immunol Rev. 2010; 238:12–22.

Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. Nature. 1996; 383:787–93.

Romagnani S. Regulation of the T cell response. Clin Exp Allergy. 2006;36: 1357–66.

Kondo M. Lymphoid and myeloid lineage commitment in multipotent hematopoietic progenitors. Immunol Rev. 2010; 238:37–46.

Pyzik A, Grywalska E, Matyjaszek-Matuszek B, Rolinski J. Immune disorders in Hashimoto’s thyroiditis: what do we know so far? J Immunol Res. 2015; <https://doi.org/10.1155/2015/979167>.

Ramos-Leví AM, Marazuela M. Pathogenesis of thyroid auto- immune disease: the role of cellular mechanisms. Endocrinol Nutr. 2016; 63:421–9.

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

Kambayashi T, Laufer TM. Atypical MHC class II-expressing antigen presenting cells: can anything replace a dendritic cell? Nat Rev Immunol. 2014; 14:719–30.

Kristensen B. Regulatory B and T cell responses in patients with autoimmune thyroid disease and healthy controls. Dan Med J. 2016;63(2): B5177.

Nagayama Y. Graves’ animal models of graves’ hyperthyroidism. Thyroid. 2007; 17:981–8.

Pelletier JP, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. Arthritis Rheum 2001; 44:1237–47.

Sakkas LI, Scanzello C, Johanson N, Burkholder J, Mitra A, Salgame P, et al. T cells and T-cell cytokine transcripts in the synovial membrane in patients with osteoarthritis. Clin Diagn Lab Immunol 1998; 5:430–7.

Scanzello CR, Sakkas LI, Johanson NA, Platsoucas CD. Oligoclonal populations of T-cells infiltrate the synovial membrane (SM) of patients with osteoarthritis (OA) [abstract]. Arthritis Rheum 1999;43 Suppl 9: S257.

Scanzello C, Sakkas LI, Johanson N, Platsoucas CD. Clonally expanded T cells in the synovial membrane of patients with osteoarthritis. Scand J Immunol 2001;54 Suppl 1:59.

Linblad S, Hedfors E. Arthroscopic and immunohistologic characterization of knee joint synovitis in osteoarthritis. Arthritis Rheum 1987; 30:1081–8.

Smith MD, Triantafillou S, Parker A, Youssef PP, Coleman M. Synovial membrane inflammation and cytokine production in patients with early osteoarthritis. J Rheumatol 1997; 24:365–71.

Koch AE, Turkiewicz W, Harlow LA, Pope RM. Soluble Eselectin in arthritis. Clin Immunol Immunopathol 1993; 69:29–35.

Loetscher P, Uguccioni M, Bordoli L, Baggiolini M, Moser B, Chizzolini C, et al. CCR5 is characteristic of Th1 lymphocytes. Nature 1998; 391:344–5.

Alsalameh S, Mollenhauer J, Hain N, Stock KP, Kalden JR, Burmester GR. Cellular immune response toward human articular chondrocytes: T cell reactivities against chondrocyte and fibroblast membranes in destructive joint diseases. Arthritis Rheum 1990; 33:1477–86.

Krishnan S, Warke VG, Nambiar MP, Wong HK, Tsokos GC, Farber DL. Generation and biochemical analysis of human effector CD4 T cells: alterations in tyrosine phosphorylation and loss of CD3 expression. Blood 2001; 97:3851–9.

Matsuda M, Ulfgren AK, Lenkei R, Petersson M, Ochoa AC, Lindblad S, et al. Decreased expression of signal-transducing CD3 chains in T cells from the joints and peripheral blood of rheumatoid arthritis patients. Scand J Immunol 1998; 47:254–62.

Liossis SN, Ding XZ, Dennis GJ, Tsokos GC. Altered pattern of TCR/CD3-mediated protein-tyrosyl phosphorylation in T cells from patients with systemic lupus erythematosus. J Clin Invest 1998; 101:1448–57.

Finke JH, Zea AH, Stanley J, Longo DL, Mizoguchi H, Tubbs RR, et al. Loss of T-cell receptor chain and p56lck in T-cells infiltrating human renal cell carcinoma. Cancer Res 1993; 53:5613–6.

Voskuyl AE, van Duinen SG, Zwinderman AH, Breedveld FC, Hazes JM. The diagnostic value of perivascular infiltrates in muscle biopsy specimens for the assessment of rheumatoid vasculitis. Ann Rheum Dis 1998; 57:114–7.

Aarvak T, Chabaud M, Miossec P, Natvig JB. IL-17 is produced by some proinflammatory Th1/Th0 cells but not by Th2 cells. J Immunol 1999; 162:1246–51.

Sebbag M, Parry SL, Brennan FM, Feldmann M. Cytokine stimulation of T lymphocytes regulates their capacity to induce monocyte production of tumor necrosis factor-, but not interleukin-10: possible relevance to pathophysiology of rheumatoid arthritis. Eur J Immunol 1997; 27:624–32.