DISCUSS THE INVOLVEMENT OF T- AND B- LYMPHOCYTES IN THE PATHOGENESIS AND PROGRESSION OF OSTEOMYELITISAND OSTEOARTHRITIS

BY

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T-lymphocytes

Analysis of enzyme-linked immunosorbent assay (ELISA) data has shown that compared with age-matched healthy controls, patients with OA show higher levels of the soluble form of CD4 (sCD4) in their serum. This suggests that peripheral T helper (Th) cells are involved in the pathogenesis of OA. Similarly, when stimulated with phorbol myristate acetate (PMA) and ionomycin, peripheral mononuclear cells from OA patients showed a higher expression of CD4 and CD8 markers than their counterparts from healthy controls. Indeed, the ratio of CD4+/CD8+ in the blood of OA patients is higher than that in the blood of healthy controls, although healthy controls and OA patients have fairly similar numbers of CD4+ and CD8+ T cells in their blood. Further evidence of the involvement of peripheral T cells in the pathogenesis of OA was provided by the discovery that the response to autologous chondrocytes of peripheral T cells isolated from OA patients is greater than of peripheral T cells isolated from controls and that this response is partially blocked by antibodies against human leukocyte antigen (HLA) classes I and II, CD4, and CD8. Interestingly, T cells in a subset of OA patients were found to recognize the peptides representing amino acid regions 16–39 and 263–282 of human cartilage proteoglycan aggrecan (PG), and peripheral blood mononuclear cells from these PG-reactive OA patients showed an increased production of pro-inflammatory cytokines/chemokines in response to PG peptide stimulation. Based on these compelling findings, the autoimmune responses of peripheral T cells may aid understanding of immune-mediated mechanisms in OA.

Enzyme-linked immunosorbent assay analysis revealed higher levels of sCD4 not only in the peripheral blood but also in the synovial fluid of patients with OA, compared with age-matched healthy controls, which suggests that Th cells in the synovial fluid are involved in the pathogenesis of OA . When stimulated with PMA and ionomycin, mononuclear cells from the synovial fluid of OA patients showed a high expression of CD4 and CD8 markers. These compelling results suggested that T cells in the synovial fluid are associated with the pathogenesis of OA. This conclusion was supported by subsequent investigations. For example, the percentage of T cells in the synovial fluid of OA patients was found to be significantly higher than that in their peripheral blood, and T cells in the synovial fluid of OA patients expressed class II HLA (an indicator of activated T cells). The percentages of CD4+ and CD8+ cells in the synovial fluid of OA patients were even similar to those found in RA patients.

T cells are the major constituents of synovial infiltrates in the membranes of OA patients, and both CD4+ T cells and CD8+ T cells have been found within synovial aggregates. For example, synovial tissue extracted from OA patients displayed perivascular CD3+ T cell infiltration at an early stage. Similarly, using immunohistochemical analysis, CD3+, CD4+, and CD8+ T cells were detected predominantly in the sublining layer and more limitedly in the deep layer of the synovium of patients with OA, whereas the presence of CD4+ T cells in the synovial sublining layer was detected more strongly in OA patients than in normal subjects. CD4+ T cells were found to be predominant among the T-cell infiltrates in the synovial tissue, and the number of CD4+ T cells was higher in the synovial sublining layer of patients with OA than in that of normal subjects. Indeed, the medial synovium of patients with knee OA has been shown to contain more CD4+ T cells than the lateral synovium. Interestingly, synovial aggregates from OA patients express CD80, an inducible costimulatory ligand involved in T-cell activation, suggesting that synovial aggregates in OA patients are areas of antigen recognition and T-cell activation. Similarly, researchers investigating 30 patients with OA found CD3+ T cell aggregates in the synovial membrane in 65% of the patients, and the activation antigens CD69, CD25, CD38, CD43, CD45RO, and HLA class II were also found in the synovial membrane. In addition, HLA-antigen D-related (DR)-expressing T cells were found in the synovial membranes of OA patients using immunohistochemical analysis, although to a lesser degree than in RA patients. The conclusion that activated T cells are aggregated in the synovial membranes of OA patients was further supported by the discovery that virtually all T cells in OA joints express activation markers, such as HLA-DR and CD69. Interestingly, OA patients older than 75 have higher percentages of CD3+, CD4+, and CD8+ cells in their synovial membranes than OA patients younger than 75. This may suggest that age is among the risk factors for OA.

Collectively, significant abnormalities in the T-cell profile have been found in the peripheral blood, synovial fluid, and synovial membranes of OA patients. Based on these findings, T cells are assumed to be associated with the pathogenesis of OA.

B-lymphocytes

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.

Project hypothesizes have shown that the interactions between the musculoskeletal and the immune system are important sources of divergence between healthy people and patients with OA. By postulation we can better understand the pathology of OA by distinguishing ageing specific changes from those that are OA specific. Recently it has shown that the immune cell composition of the blood of OA patients is quite divergent 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 OA. However, B-cell infiltration in OA is quite independent of T-cells and the presence of germinal centre like structures is rarely observed.

 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 OA) 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 will be used to establish the role of TLR activation on B-cell maturation and effect on the activation of XBP-1. Gene expression profiling will address the pathways implicated in this alternative maturation process including XBP-1 and genes of the B-cell receptor and immunoglobulin rearrangement pathways. These profiles will be 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 OA patients and from OA synovial tissue to assess the mean by which B-cells mature and produce IgGs (i.e. T-cell dependent or independent pathways).

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