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SECTION 1: CELL BIOLOGY AND PHYSIOLOGY Guest editor: J C W Edwards

Synovial macrophages

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The mononuclear phagocyte system in the synovial membrane is represented by specialised lining cells of the synovial intima and macrophages in the subintima and synovial fluid.[1] In common with mononuclear phagocytes in other tissues, they are derived from a common bone marrow precursor and show certain functional and cytochemical characteristics. The most distinctive feature of these cells is their avid phagocytic ability, but their other functions include induction and regulation of hormonal and cellular immune responses, and formation and release of a large number of secretory products.

The synovial membrane contains a distinctive intimal lining, one to two cells thick, composed of specialised synovial lining cells (SLCs). At least two cell types have been demonstrated ultrastructurally in the synovial lining:[1 2] type A (macrophage like cells) which have prominent filopodia, vacuoles, vesicles, and poorly developed rough endoplasmic reticulum; and type B (fibroblast like) cells which have a well developed rough endoplasmic reticulum, and few vesicles, vacuoles or cell processes. A type C cell has also been identified, with features intermediate between those of type A and type B cells. These differences in ultrastructural morphology led to the hypothesis that A and B cells represent a single cell type with morphology reflecting functional status, and that the type C cell represented a precursor of the A and B cells.[3] However, the distinct origin and lineage of the two cell types in the synovial membrane was established using radiation chimaeras of normal and beige mice which showed giant granules in 1–7% of ultrastructurally type A SLCs in the normal synovium.[4] This was supported by analysis of the immunophenotype of SLCs, which showed the presence of several characteristic macrophage markers such as HLA-DR, Fc and C3 receptors on SLCs,[5 6] in addition to strong expression of a wide range of leucocyte/macrophage antigens on both SLCs and subintimal macrophages (table).[7–9] These include expression of leucocyte common antigen (LCA), an epitope expressed by all nucleated derivatives of the haemopoietic stem cell, and monocyte/macrophage markers such as CD14 and CD68. In the normal (non-hyperplastic) synovial lining, it was found that fewer than 10% of SLCs are LCA positive;[8] this shows that the predominant cell type in the normal synovial membrane is the type B cell, a finding which accords with those of both radiation chimaera and ultrastructural studies.[4 10] Type A and type B cells can also be separated on the basis of cytochemical staining for uridine diphosphoglucose dehydrogenase, a marker of fibroblast-like SLCs, and non-specific esterase (NSE), a macrophage marker.[11]

Some leucocyte/macrophage immunophenotypic markers expressed by human synovial lining cells

1. 'Macrophage' markers on SLCs—Fc receptor
   —C3b receptor
   —Non-specific esterase
   —MHC class II antigen
2. Leucocyte/macrophage markers strongly expressed by SLCs
   CD45 (leucocyte common antigen)
   CD11b (CR3), CD13, CD14, CD16 (FcRIII), CD18, CD32 (FcRII)
   CD54 (ICAM-1), CD64 (FcRI), CD68, HLA-DR

A thickened or 'hyperplastic' synovial intima is a common histological finding in several forms of arthritic disease. The cellular mechanisms underlying its formation are not fully established. SLCs are known to be capable of cell division;[12 13] tissue macrophages are also known to have a limited capacity for proliferation and further differentiation.[14] However, both cellular kinetic and immunophenotypic studies indicate that formation of a thickened synovial intima is largely the result of recruitment of mononuclear phagocytes. Mitoses are rarely seen amongst SLCs in inflammatory synovitis, and there is very low incorporation of tritiated thymidine or Ki-67 (nuclear proliferation antigen) activity in SLCs of the rheumatoid synovium.[13 15 16] Immunophenotypic studies also show that the number of LCA and macrophage marker positive cells is greatly increased in the rheumatoid synovial lining.[8] Synovial giant cells in the hyperplastic synovium in rheumatoid arthritis (RA) also show a macrophage phenotype, indicating that these cells are a type of macrophage polykaryon. Increased numbers of LCA/macrophage marker positive SLCs can also be found in the synovium in osteoarthritis (OA), but these generally have a more patchy distribution in the synovial intima.[8]

SLCs and subintimal macrophages do show some differences in expression of macrophage associated antigens.[9] Absence and decreased expression of CD25 (interleukin-2 receptor), CD35 (C3b receptor) and CD34 on SLCs relative to subintimal macrophages may reflect differences in the functional status or micro-environment of the two cells. It is possible that differentiation/maturation of subintimal macrophages to SLCs is associated with the loss and possible acquisition or enhanced expression of particular macrophage antigens; however, the precise pathway which monocytes recruited into the joint follow as synovial macrophages in the subintima, intima, and joint cavity has not been fully established. In addition, the

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precise relationship between synovial macrophages and dendritic cells, which are poorly phagocytic, specialised antigen-presenting cells, needs to be determined. Burmester *et al*[17 18] noted differential expression of macrophage antigens in the RA synovial lining, in particular an increase in cells of dendritic morphology and immunophenotype (HLA-DR positive, FcR negative); they also noted an increase in cells of similar phenotype in the subintima, particularly in the vicinity of perivascular lymphoid infiltrates. Broker *et al*[19] also noted microanatomical differences in the expression of NSE, CD14 and FcR amongst SLCs in the synovial intima; these and other studies show significant numbers of macrophages in the inflamed synovium, and apparently no correlation between the number of macrophages and the degree of any lymphocytic infiltrate.[20]

Cell-cell and cell-matrix interactions through cell adhesion molecules (CAMs) are important in the maintenance and organisation of the normal synovial membrane. A large number of integrin and non-integrin receptors have been identified on intimal and subintimal cells in the normal synovial membrane.[21 22] Immunohistochemical overlap with synovitis and immunophenotypic heterogeneity for HLA-DR and other adhesion molecules have been noted, but upregulation of CAM expression by SLCs and subintimal cells has also been noted in certain forms of arthritis. Increased expression of β_2 integrin leucocyte adhesion molecules, CD11a, CD11b, and CD11c (particularly the latter) on mononuclear phagocytes in RA has been reported;[20 23 24] these molecules are important in determining leucocyte emigration into inflamed tissues. Other leucocyte and endothelial CAMs upregulated in the inflamed synovium are vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and endothelial leucocyte adhesion molecule-1 (ELAM-1; now known as E-selectin), in addition to lymphocyte function associated antigen-3 (LFA-3) and ICAM-3.[24-26] Expression of a number of these CAMs can be upregulated by cytokines produced by inflammatory cells, notably macrophages, in the inflamed synovium. Synovial macrophages are derived from circulating monocytes which pass through tall endothelial cells of post capillary venules before migrating to their tissue location in the intima or subintima. These macrophages appear to be activated—that is, they show a quantitative change in the level of expression of certain gene products that enable them to carry out a variety of complex functions.[27] Differences in the immunophenotype of macrophages in the synovial intima and subintima of RA and OA are likely to point to differences in the activation state of these cells: circulating monocytes in RA have been reported to show enhanced metabolic and phagocytic activity, and to express surface markers consistent with macrophage activation;[28] however, there is also evidence to show that monocytes become fully activated and differentiate into more mature macrophage like cells in the rheumatoid joint.[29]

A key role for activated macrophages (and fibroblasts) has been postulated in the pathogenesis of RA. T cells are not fully activated in RA, and at both the protein and mRNA level, macrophage derived cytokines such as interleukin-1(IL-1) and tumour necrosis factor α (TNFα), are abundant, whereas T cell cytokine products are not.[30] Thus, in contrast to the T cell centred models of RA pathogenesis, in which proliferation of antigen specific T cells determines other manifestations of rheumatoid synovitis such as B cell stimulation, leucocyte infiltration, and elaboration of cytokines, a central role for synovial macrophages and fibroblasts is envisaged[31] in which, by paracrine and autocrine mechanisms involving release of cytokine products, there is stimulation and maintenance of the inflammatory changes in the rheumatoid synovium. Through secretion of cytokines, synovial macrophages can stimulate fibroblast proliferation and activity, which can lead to further cytokine, collagenase, and prostaglandin release, enhance HLA-DR expression on synovial cells, and activate T and B cells. IL-1 and TNFα production by macrophages also enhances the ability of circulating leucocytes to attach to and pass through tall endothelial cells of post capillary venules by inducing expression of CAMs such as E-selectin, ICAM-1, VCAM-1 and LFA-3.[30-32] Macrophage and fibroblast cytokine products are also likely to contribute to the induction of new blood vessel formation in rheumatoid synovial tissues. Destruction of bone and cartilage in RA (and other joint disease) is also likely to be associated with cytokine release by activated macrophages and fibroblasts.[33] These cells, rather than T cells, predominate at the synovium-cartilage junction where joint erosion occurs. Release of IL-1 and TNFα by synovial macrophages stimulates release of collagenase, elastase, plasminogen activator, and prostaglandins, which also play a role in tissue destruction. Macrophage and fibroblast derived cytokines are also known to enhance osteoclastic bone resorption indirectly (via osteoblast stimulation). In addition, it is possible that synovial macrophages themselves may differentiate into osteoclast like bone resorbing cells and directly cause bone resorption, as it has been shown that inflammatory macrophages have this capability when stimulated by bone stromal cells in the presence of 1,25,dihydroxyvitamin D_3[34]—itself synthesised by synovial fluid macrophages and present in increased amounts in joint conditions associated with marked bone destruction.[35] The figure shows some of the means whereby synovial macrophages and fibroblasts are likely to influence arthritic disease.

Similar mechanisms may also account for the cell and tissue changes and bone and joint destruction found in other forms of synovial pathology in which macrophages comprise the major inflammatory component, such as infective or sarcoid like granulomatous synovitis, and crystal deposition diseases; they are also thought to play a role in dialysis amyloid arthropathy, in which discrete

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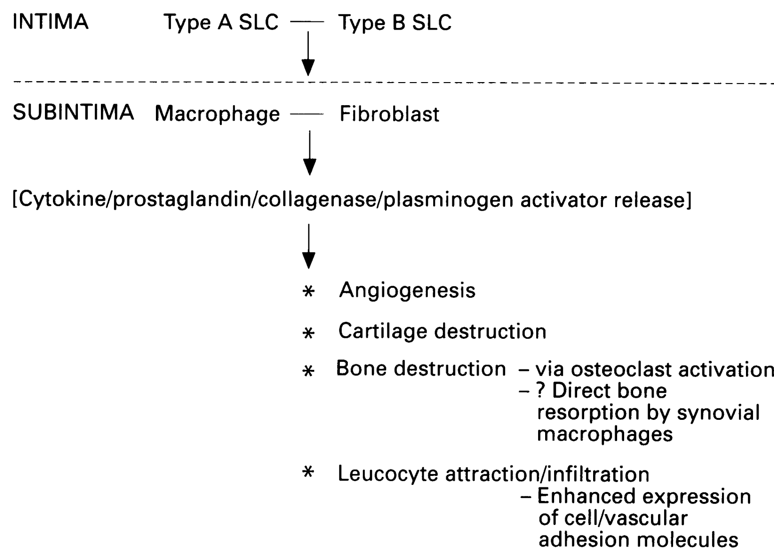

*Influence of intimal and subintimal macrophages (and other synovial cells) on the pathobiology of rheumatoid disease. SLC = Synovial lining cells. *Activation of T cells and B cells.*

collections of macrophages and macrophage polykaryons around β_2 microglobulin amyloid deposits, and a more diffuse heavy macrophage infiltrate are not uncommonly found. In addition, tumour like lesions of the synovium such as pigmented villonodular synovitis, characterised by an increase in macrophages and macrophage polykaryons in response to haemosiderin and other bood products, can also be associated with bone and joint erosions.

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