INFLAMMATION is defined by the association of redness, heat, pain and swelling, blood vessel dilatation and influx of bloodstream cells at the site of injury. However, these events are the consequences of biochemical processes that activate cells which, in turn, become capable of reacting to a range of molecules, e.g. cytokines, eicosanoids and reactive oxygen species, acting on neighbour cells. Thus, these activated cells are the initial reactors in inflammation.

The major tissue that becomes inflamed in rheumatoid arthritis (RA) is the synovium, leading to multiple layers of synovial lining cells and a rich capillary and sensory nerve network. This produces dilatation of blood vessels and an influx of blood cells, giving the typical aspect of inflammation. By of biochemical processes that activate cells which, in turn, become capable of reacting to a range of molecules, e.g. cytokines, eicosanoids and reactive oxygen species, acting on neighbour cells. Thus, these activated cells are the initial reactors in inflammation.

The major tissue that becomes inflamed in rheumatoid arthritis (RA) is the synovium, leading to multiple layers of synovial lining cells and a rich capillary and sensory nerve network. This produces dilatation of blood vessels and an influx of blood cells, giving the typical aspect of inflammation. By contrast, articular cartilage is avascularized and is not innervated, and is made up of only one type of cell, chondrocytes, plus an abundant extracellular matrix in which these cells are embedded. This prevents chondrocyte proliferation and the penetration of cells, so that a rheumatoid joint exhibits inflammation of the synovial tissue, and apparently inactive articular cartilage, with or without bone erosions. Hence, adult articular cartilage was initially considered to be a tissue with a very poor metabolic capacity that only synthesized collagens during growth and had a low turnover of proteoglycans. Cartilage was found to have a much more important capacity to produce proteases, leading to an astatic homeostasis. Since the mid-1980s, molecular biology has shown that the chondrocytes produce several molecules implicated in cartilage destruction, and there is evidence that cartilage plays an active part in joint inflammation.

A few years ago, Robin Poole [1] noted that joint inflammation usually subsides when all the cartilage is removed from a joint, suggesting that cartilage is involved in joint inflammation. Since then, many in vitro studies have demonstrated that chondrocytes can produce all sorts of pro-inflammatory molecules. Interleukin-1 (IL-1) and tumour necrosis factor-z (TNF-z) are produced by activated chondrocytes. They themselves are able to activate different intra-cellular pathways via their receptors on chondrocytes, leading to the synthesis of pro-inflammatory mediators [2–5]. Our studies and those of others have shown that IL-1 induced the production of prostaglandin E2 by chondrocytes because of IL-1-induced overproduction of type II secreted phospholipase A2 and cyclooxygenase-2 (COX-2) by specific transcriptional and post-transcriptional mechanisms [6–8]. COX-2 is regulated by nitric oxide (NO) [9], and NO is overproduced by chondrocytes via an IL-1-induced iNOS synthase synthesis [10]. Therefore, a network of pro-inflammatory mediators in cartilage seems to be able to act on its neighbour cells, independently of the synovium.

Geiler et al. [11] have shown that cartilage erosion appears when the cartilage contacts the synovium. This demonstrates the importance of the synovium in

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**‘RHEUMATOID CHONDritis’ OR THE PLACE OF CARTILAGE IN RHEUMATOID INFLAMMATION**

the cartilage destruction in RA. Cartilage, in turn, could cause synovial inflammation via the pro-inflammatory mediators secreted by chondrocytes. Histological studies of cartilage–pannus junctions (CPJ) show several cell types, including monocyte-macrophages, fibroblasts, mast cells, polymorphonuclear cells, T cells and chondrocytes.[12] Chondrocytes could act specifically on these cells types: IL-1- and TNF-α-stimulated chondrocytes can produce IL-8, which plays a direct role in PMN activation.[13, 14]; activated chondrocytes bear class II HLA molecules, which could interact with CPJ-T cells[15]; monocyte influx and activation is mediated by monocyte chemoattractant protein-1 (MCP-1), a protein produced by activated chondrocytes[16]; lastly, there may be direct contacts between chondrocytes and CJP cells, since adhesion molecules have been found on activated chondrocytes[17, 18]. IL-6, IL-11, leukaemia inhibitory factor, tumour necrosis factor-stimulated gene 6, granulocyte macrophage colony stimulating factor and complement components are also implicated in pro-inflammatory events and produced by activated chondrocytes[19–24].

The relative importance of pro-inflammatory mediators synthesized by synovium and those produced by cartilage has not yet been investigated. While more may be produced by the synovium because there are more cells in the pannus, the cartilage matrix is able to retain these molecules, and so could work as a reservoir[25].

There are now sufficient published data to indicate that the RA cartilage is an actor in joint inflammation, capable of initiating and/or propagating the rheumatoid synovitis, despite the absence of vessels, or chondrocyte proliferation. Chondrocytes should, therefore, be considered as an active partner in a flare of RA, along with synovial cells, endothelial cells and lymphocytes. These other cells have been studied more because they are easier to manipulate. This extended idea should lead to research for new drugs with anti-inflammatory and anti-resorptive actions specifically targeted to the cartilage, which is the main articular tissue. A search for inhibitors of the specific intracellular pathways involved in chondrocyte activation could be one of these areas.

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