Are fibroblasts involved in joint destruction?

T Pap, I Meinecke, U Müller-Ladner, S Gay

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that primarily affects the joints and results in the progressive destruction of articular structures, particularly cartilage and bone. Notably, the joint destruction is a prominent feature of disease that not only distinguishes RA from other arthritides but also determines its outcome in the majority of affected individuals.

SYNOVIAL FIBROBLASTS IN RA

Synovial fibroblasts in the most superficial lining layer of the hyperplastic RA synovium have been assigned an important role in the pathogenesis of RA and associated with key processes leading to the degradation of extracellular matrix. It has been understood that these cells exhibit an altered morphology and are characterised by changes in their behaviour that show certain similarities to tumours. Therefore, the phenotype of these cells has been termed “transformed appearing”, “tumour-like” or—reflecting the clear differences with malignancies—“activated”. As part of a cellular network, RA synovial fibroblasts are involved in the destruction of extracellular matrix both by direct mechanisms and through interaction with neighbouring cells such as macrophages. Thus, it has been demonstrated that RA synovial fibroblasts release large amounts of the ligand for the receptor activator of nuclear factor κB (RANKL), which mediates the differentiation of bone resorbing osteoclasts from their macrophage precursors. Direct degradation of extracellular matrix by RA synovial fibroblasts is mediated through the attachment to cartilage and subsequent release of matrix degrading enzymes, particularly matrix metalloproteinases (MMPs) and cathepsins.

ACTIVATION OF RA SYNOVIAL FIBROBLASTS

Although inflammatory cytokines such as tumour necrosis factor-α (TNFα) have been demonstrated to stimulate RA synovial fibroblasts to produce such matrix degrading enzymes, the activation of these RA synovial fibroblasts is maintained even in the absence of continuous stimulation by proinflammatory factors. This notion is derived from different in vitro studies as well as from data on the severe combined immunodeficient (SCID) mouse model of rheumatoid cartilage destruction. Initially, this model was designed to investigate the fate of inflammatory cells, particularly lymphocytes in the inflamed RA synovium. However, by implanting rheumatoid synovial tissue into SCID mice, it was shown that lymphocyte infiltrates disappear with time, whereas lining layer synoviocytes survive. Interestingly, these RA synovial fibroblasts not only survived in SCID mice recipients but also maintained their characteristic biological features. Based on these observation, the SCID mouse co-implantation model was developed as a new model for studying molecular mechanisms of rheumatoid joint destruction in vivo. To imitate the situation in a rheumatoid joint, human RA synovium was implanted together with normal human cartilage under the renal capsule in SCID mice. It was shown that RA synovial tissue and normal human cartilage can be kept in SCID mice for more than 300 days with the RA synovium maintaining its invasive growth and progressive cartilage destruction. On histological examination, the vast majority of synovial cells found at sites of cartilage invasion resembled activated synovial fibroblasts.

To study specifically the molecular characteristics of these fibroblasts as well as their contribution to cartilage degradation, normal human cartilage was implanted together with isolated synovial fibroblasts from patients with RA in a next step. As SCID mice do not reject these implants, the SCID mouse model has helped to analyse the matrix degrading properties of RA synovial fibroblasts in the absence of both human lymphocytes and macrophages. In contrast to osteoarthritis or normal synovial fibroblasts, RA synovial fibroblasts maintained their aggressive phenotype, especially at sites of invasion and also maintained their ability to express vascular cell adhesion molecule (VCAM)-1 and other activation markers. Using in situ hybridisation techniques to examine the presence of mRNA for matrix degrading enzymes a number of cartilage degrading proteases were demonstrated. In contrast, much fewer or none of these matrix degrading enzymes could be found, when normal, osteoarthritic synovial fibroblasts, or deroal fibroblasts were examined. These results indicated an active role of synovial fibroblasts in the joint destruction of RA. Furthermore, they suggested that RA synovial fibroblasts were not just passively responding to stimuli from the inflammatory environment but also maintaining their activated and aggressive phenotype in the absence of continuous stimulation from human macrophage or lymphocyte derived cytokines.

ROLE OF SYNOVIAL FIBROBLASTS IN MATRIX DEGRADATION

Interestingly some experiments in the SCID mouse model suggest that activated fibroblasts are capable of resorbing not only cartilage but also bone. This was initially shown for activated fibroblasts from the synovial-like interface membrane around loose joint prostheses, which show similarities to RA synovial fibroblasts. Specifically, we demonstrated that fibroblasts developing at the interface of bone and prosthesis in aseptic loosening prosthesis are capable of superficial bone erosion both in vitro and in vivo. At co-implantation with femoral bone into SCID mice, such fibroblasts formed resorption lacunae and even reshaped the osseous matrix. The conclusion that osteoclasts are not required was derived from the experimental setting of the SCID mouse studies that excluded the presence of human macrophages and osteoclasts in the implants. In addition, immunohistological analysis using antibodies specific for human fibroblasts demonstrated the human nature of cells resorbing the co-implanted bone. These data were confirmed in vitro, where isolated fibroblasts produced resorption pits when cultured on dentine for four weeks. Compared with
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With the degree of synovial inflammation. Recently, a close correlation between the expression of MMP 1 and the invasive growth of RA synovial fibroblasts has been found, but the specific contribution of individual MMPs to matrix degradation is only partly understood. Using gene transfer of ribozymes to MMP 1 we demonstrated recently that the specific inhibition of MMP 1 significantly reduces the production of these enzymes in RA synovial fibroblasts and inhibits the invasiveness of the cells in the SCID mouse model. In this study, transduction of RA synovial fibroblasts with ribozymes to MMP 1 decreased significantly the production of MMP 1 without affecting other MMPs such as MMP 9 and MMP 13. MMP 1 specific ribozymes reduced not only the spontaneous production of MMP 1 but also prevented the lipopolysaccharide (LPS) and TNFα induced increase in MMP 1 production. Inhibition of MMP 1 was maintained for at least two months and accompanied by a reduction of the invasiveness of RA-SF in the SCID-mouse model by about 50%.

Normally, MMP activity is balanced by the naturally occurring tissue inhibitors of metalloproteinase (TIMPs) that interact irreversibly with MMPs. TIMPs are synthesised and secreted by chondrocytes, synovial fibroblasts, and endothelial cells. In situ hybridisation studies demonstrated striking amounts of TIMP 1 mRNA in the synovial lining of patients with RA, but it is widely accepted that the molar ratio of MMPs to TIMPs rather than the absolute levels of TIMPs are crucial for joint destruction. In RA, the amount of MMPs outweighs that of TIMPs, allowing destruction to take place. In line with this concept, we have shown that the overexpression of TIMP 1 and TIMP 3 by gene transfer may result in a marked reduction of the invasiveness of RA synovial fibroblasts. Interestingly, TIMP 3 not only inhibits the degradation of extracellular matrix but shows a number of features that are distinct from other TIMPs. Thus, TIMP 3 can prevent the shedding of cell membrane proteins such as the TNF receptor, the interleukin (IL)-6 receptor, and of TNFα-converting enzyme (TACE). Another interesting feature of TIMP 3 is its ability to induce apoptosis in different cell types. In this context, we have shown most recently that in addition to its general pro-apoptotic function, TIMP 3 can sensitise RA synovial fibroblasts to apoptosis induced by Fas ligand when expressed through adenoviral gene transfer. Moreover, adenoviral delivery of TIMP 3 reversed completely the inhibiting effects of TNFα on apoptosis in RA synovial fibroblasts. These findings indicate that overexpression of TIMP 3 in RA synovial fibroblasts may have beneficial effects both by inhibiting matrix degradation and by facilitating cell death.

CONCLUSION

Collectively, these data suggest that RA synovial fibroblasts contribute significantly to the joint destruction in RA and exhibit features of stable cellular activation of which the increased production of MMPs is a prominent one. Inhibition of MMPs, therefore, is an promising strategy to interfere with the destructive potential of RA synovial fibroblasts. Strategies to achieve this goal include the inhibition of signalling molecules that regulate the expression of MMPs as well as the delivery of molecules that inhibit MMPs directly—either by interfering with its mRNA or by acting as antagonists.

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