also expressed by a number of cells in the inflammatory system. It is likely that release of osteopontin in joint destruction will influence the inflammatory response.

Other bone proteins with a capacity to bind $\alpha v \beta 3$ include BSP and osteoadherin. Their role in bone turnover and interactions with other tissues remains to be elucidated, but available data indicate primary functions in bone formation.

SP0099 SYNOVIAL FIBROBLASTS DEGRADING CARTILAGE AND BONE

^{1,2}T Pap, ¹Y Shigeyama, ^{1,3}U Müller-Ladner, ¹S Ohtsu, ⁴W Van der Laan, ⁵K Aupperle, ^{1,3}J Schedel, ⁶W Aicher, ⁵G Firestein, ¹RE Gay, ¹S Gay. ¹Center of Exp. Rheum., Department Rheum., University Hospital Zurich, Switzerland; ²Department of Exp. Rheum., University Hospital Magdeburg, Germany; ³Department of Medicine I, University Hospital Regensburg, Germany; ⁴Leiden University Medical Center, Leiden, The Netherlands; ⁵Division Rheumatology, Allergy and Immunology, UCSD School of Medicine, San Diego, USA; ⁶Bas Science Res. Lab., Department Orthop. Surg., University Hospital Tübingen, Germany

10.1136/annrheumdis-2001.43

The progressive destruction of cartilage and bone is one of the most characteristic features of rheumatoid arthritis (RA). It results from the concerted action of different cell types such as T cells, fibroblasts and macrophages that through direct contact as well as the release of cytokines form a cellular network in the inflamed synovium. Research of the last decade has provided evidence that RA synovial fibroblasts (RA-SF) contribute significantly to disease and play a major role in both initiating and driving the destructive process. It has been understood that intrinsic cellular *activation*, alterations in *apoptosis* and the *attachment* to cartilage and bone are critical prerequisites for the degradation of extracellular matrix.

The degradation of articular cartilage by activated RA-SF has been investigated in different *in vitro* and animal models. Among the latter, the SCID mouse model of RA has been used intensively to clarify the specific role of synovial fibroblasts in rheumatoid cartilage destruction. In this model, RA-SF are co-implanted with normal articular cartilage into severe combined immunodeficient (SCID) mice. As these mice do not reject the implants, the model allows studying the degradation of articular cartilage by RA-SF in the absence of human inflammatory cells. From the SCID mouse model it has been learnt that RA-SF maintain their activated phenotype in the absence of continuous inflammatory stimulation and progressively degrade cartilaginous matrix. As demonstrated by gene transfer experiments, modulation of intracellular signalling pathways such as the Ras-Raf-MAPK pathway, the NF-kappa B transcription factor and the p53 tumour suppressor gene alter the aggressive behaviour of RA-SF in the SCID mouse model of RA.

However, research has also demonstrated clearly that proinflammatory cytokines as produced by various cells in the rheumatoid synovium further enhance the aggressive potential of RA-SF. Apart from TNF alpha, IL-1, and IL-1 dependent pathways appear to play a central role.

It is now well established that RA-SF destroy the articular cartilage directly through the release of matrix degrading enzyme such as matrix metalloproteinases (MMPs), cathepsins and serine proteases. While several of these enzymes have been identified in the rheumatoid synovium and demonstrated to contribute to cartilage degradation, the specific role of individual members of these families is still poorly understood. In addition, despite a clear understanding of general mechanisms that regulate the

expression of MMPs and cathepsins, specific pathways by which these enzymes are upregulated differentially in the course of disease need clarification. Current efforts focus on the modulation of enzymes that apart from degrading extracellular matrix directly, play a major role in activating other matrix degrading enzymes. Membrane-type MMPs (MT-MMPs) as well as the Plasmin system appear promising candidates for such approaches.

So far, fibroblasts have been associated with bone resorption mainly by indirect mechanisms such as the release of factors that enhance osteoclast activity and facilitate the differentiation of macrophages into osteoclast-like cells. Thus, fibroblasts of the rheumatoid synovium constitute a major source of the osteoclast differentiating factor (ODF) that appears to play a central role in the differentiation and activation of osteoclasts. However, recent data indicate that specific populations of activated fibroblasts such as from the synovial like interface membrane around loose joint prostheses are also capable of resorbing bone *in vivo* without the help of osteoclasts. Upon stimulation, such fibroblasts release large amounts of acidic components that may account for their ability to decalcify bone prior to its degradation. Using RT-PCR, *in situ* hybridization and immunotransmission electron microscopy, we have been able to demonstrate that these cells express a vacuolar type ATPase (v-ATPase) on their cell surface that has been implicated in the H⁺ secretion by different cell types. It is concluded that subtypes of activated fibroblasts may not only enhance but also actively contribute to the bone resorption. The question of whether this applies also to RA-SF or is associated with different ways of cellular activation needs to be determined.

Review session N° 4: The kidney in systemic R. D. – Saturday 16 June, 10.00-11.45/ Forum Hall

SP0100 PATHOLOGIC CLASSIFICATION OF LUPUS NEPHRITIS

D Ferluga. Institute of Pathology, Faculty of Medicine University of Ljubljana, Ljubljana, Slovenia

10.1136/annrheumdis-2001.44

A myriad of autoantibodies, particularly those against dsDNA, have been found to be involved in the production of a large heterogeneous set of immune complexes whose deposition in various organs, especially kidneys, appears to play a major role in triggering tissue lesions and an inflammatory response in systemic lupus erythematosus (SLE). In our series of 379 kidney biopsy and autopsy samples from SLE patients, immune deposits were demonstrated by traditional immunofluorescence in the glomeruli (99.0%) and characteristically also in the tubulo-interstitial compartment (57.4%) and extraglomerular vessels (64.4%).

Other pathogenetic immune mechanisms, e.g. anti-phospholipid antibodies and anti-neutrophil cytoplasmic antibodies, appear to be additionally involved, especially in triggering thrombosis and/or necrotizing glomerular lesions, respectively. Furthermore, nonimmune mechanisms, hyperperfusion and hyperfiltration associated with arterial hypertension and severe proteinuria as well as hyperlipidemia, play a more or less significant role in the progression of lupus renal disease. Several