

RELEVANCE OF APOPTOSIS AND PROLIFERATION IN RHEUMATOID ARTHRITIS

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Destruction of joint is a dramatic point in rheumatoid arthritis (RA). By definition, RA is an inflammatory disease and it seems obvious to consider immune inflammation responsible for destruction, as suggested by a large body of facts, e.g., in RA neutrophils are apparent in the synovial fluid. Several authors see the effectors of joint destruction in the proteases of these neutrophils. As early as 1965, Bywaters and Ansell¹ emphasized that neutrophils did not occur in the synovial tissue in RA. This is consistent with our observations over years, yet, according to our experience, there also are frequent bacterial superinfections that manifest as infiltration by neutrophils. The quantity of proteases turned into the synovial fluid in RA is, however, rather low as they have been paralyzed and neutralized by the inhibitors TIMP and macroglobulin. In the course of bacterial arthritis, however, the proteases of such masses of neutrophils exceed the capacity of the inhibitors and thus the articular cartilage will be destroyed.

The content of T and B lymphocytes in the synovial membrane in RA has led to the assumption that this cell infiltration may play a decisive role in joint destruction. For years, publications on the hypothetic role of lymphocytes predominated in the literature and rheumatologic congress reports. Yet, the real mechanism of destruction still remains to be clarified. Only the studies by Dingle *et al.*² have shed some more light on the issue. With the discovery of catabolin, later IL-1, a substance has been identified through which chondrocytes are able to induce secretion of proteases, and thus degrade the surrounding matrix. This concept of chondrocytic chondrolysis was quite enthusiastically accepted³. However, the minimal damages in the microscopic field failed to provide any explanation for joint destruction.

Over time, a wide array of cytokines have been discovered, TNF alpha being most prominent of them. A whole spectrum of effects have been ascribed to cytokines, how-

ever, almost exclusively based on the results of *in vitro* experiments. These results are interesting indeed, yet offering no explanation for the mechanism of joint destruction either.

The pathogenetic research has gained a new impulse through the discovery of apoptosis as programmed cell imminent death, whereas apoptosis disturbances have offered a welcome explanation for the multiplication of cells in the synovial membrane, based on the idea that pathologic accumulation of cells is achieved through different kinds of disturbances of regular apoptosis in the synovial membrane (Fig. 1)⁴.

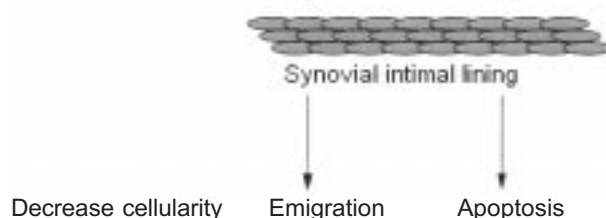


Fig. Determinants of synovial lining hyperplasia. The cellularity of the intimal lining is determined by the sum of cell migration into the tissue and proliferation minus cell death and emigration from the joint⁴.

Therefore, it should be taken in consideration that the life span of fibroblasts is estimated to several years in contrast to that of macrophages, estimated to months. This cell accumulation in the synovial membrane arising from apoptosis disturbances has been considered a source of TNF alpha and other cytokines, as proved by *in vitro* investigations.

These *in vitro* studies constitute the 2005 state-of-the-art in the field, yet they still offer no explanation for the pathogenesis of joint destruction. TNF alpha and other

cytokines are secreted in any type of inflammation, including any type of joint inflammation. However, in our material collected over years and including approximately 90,000 patients suffering from different rheumatic diseases we did not observe any articular cartilage lesions of nonbacterial inflammation or high inflammatory processes like those seen in rheumatic fever or reactive arthritis. Fortunately, the joint is protected by inhibitors. Otherwise, we all would already suffer from arthrosis at age 20.

Unfortunately, the research in apoptosis, based on *in vitro* studies, has pushed a systematic morphological analysis of RA process away. Thus, there are only few sporadic investigations of synovial membrane lesions in RA and other rheumatic disorders available. This is in part due to the fact that many investigators did not gain access to the proper process of tumor-like proliferation (TLP, Deutsches Krebsforschungszentrum) responsible for destruction.

We analyzed synovial tissue from 4,480 patients, obtained intraoperatively during the 1991-2004 period, and joint segments (articular cartilage and bone) from 288 patients suffering from RA, through which we were able to divide the course of the synovial process in RA into 4 stages. So, we could prove TLP process, singly specific for RA, in only 2% of cases. The other 3 stages correspond to an unspecific granulation tissue. Accordingly, we conclude that the stage responsible for destruction is very short-lived. The chance to meet it in a small number of specimens (6-

23 in the literature) is minimal. We have also confronted these 4 stages with the disease duration in patients, which yielded no correlation, thus there is no doubt for us about the short life span of the TLP process.

The short life of this aggressive cell formation is understandable, as on the one hand this compact formation does not possess any blood vessels, and on the other hand the large vital, newly formed cells show a high metabolic activity. In contrast to this, the true tumor grows as slowly as the formation of new vessels can keep up with its development.

References

1. BYWATERS EGL, ANSELL BM. Monoarticular arthritis in children. *Ann Rheum Dis* 1965;24:116-22.
2. DINGLE JT, SAKLATVALA J, HEMBRY R, TYLER J, FELL HB, JUBB R. A cartilage catabolic factor from synovium. *Biochem J* 1979;184:177-80.
3. AYDELOTTE MB, SCHLEYERBACH R, ZECK BJ, KUETTNER KE. Articular chondrocytes cultured in agarose gel for study of chondrocytic chondrolysis. In: KUETTNER KE, SCHLEYERBACH R, HASCALL VC, eds. *Articular cartilage biochemistry*. New York: Raven Press, 1986:235-56.
4. FIRESTEIN GS. Invasive fibroblast-like synoviocytes in rheumatoid arthritis – passive responders or transformed aggressors? *Arthritis Rheum* 1996;39:1786.