ONCOLOGICAL PROLIFERATIVE MECHANISMS IN RHEUMATOID ARTHRITIS AND SERONEGATIVE SPONDYLARTHRITIDES

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As a basic principle, two mechanisms are held responsible for structural damage:

1. the regulated inflammation process,
2. the irregular autonomous proliferation of cells.

The inflammation is commonly seen as the principal tissue and organ damaging mechanism, because it is accompanied by noticeable clinical symptoms, mainly pain.

An accumulation of cell elements, i.e. a swelling occurs along with the autonomous proliferation process. So, it has an oncological character, however it usually runs asymptomatically.

With increasing knowledge of the complexity of the inflammation process and the branched network of its components, new possibilities to intervene in its courses arise continuously, for example TNFα receptor blockers. Therefore, the expectation arises to be able to intervene in the pathological basic process as well and approach the joint destruction, which is the core of RA. But actually, the resulting therapies do not transcend the inflammation network.

In addition, the importance of autonomous proliferation processes is underestimated. Generally, they are only noticed as mechanisms of defined benign or malignant tumors.

Due to the fact that autonomous proliferation processes are often accompanied by clinically dominating inflammation phenomena, they remain unidentified as actual pathomechanisms.

The inflammation process generally, is a temporary reaction of the organ to outside animated or unanimated irritations with body-own defense mechanisms. The accompanying pain has a signaling character.

The oncological proliferative process is an autonomous procedure released by body-own factors and leading to the formation of new structures. Two examples are:

1. Rheumatoid Arthritis (RA)
2. Psoriatic Arthritis (PSA) and Ankylosing Spondylitis (AS) as representatives of the Seronegative Spondylarthritides (SSA)

The signaling character is missing for the oncological proliferative process since it is, generally, painless.

Autonomous oncological proliferation processes (OPP) in RA

The synovial process in RA has a nonspecific as well as a specific component. The immunological inflammation name-giving for the disease is nonspecific. It is responsible for the pain symptomatology, whereas for the integrity of the joint it is harmless. Nevertheless this clinically remarkable component masks the actual drama of RA: the specific oncological proliferative process, which courses autonomously and independently of the inflammation process and is responsible for joint destruction.

It runs in stages. The proliferating cells are not normal elements of the organism. Regarding their phenotype and ultrastructure they are not fibroblasts, macrophages or lymphocytes. It is still unclear whether these cells are descendants of undifferentiated fibrocytes or migrated undifferentiated mesenchymal progenitor cells, which develop de novo and proliferate triggered by morphogenetic genes. Despite their uncertain origin, an overexpression of the oncogenes c-myb, c-myc, c-ras, and c-fos can be proved in these cells (1).

The compact formation of these oncologically proliferated cells in the synovial membrane would, actually, be marginal. The disaster for the joint, however, results from the fact that they leave the synovial tissue and penetrate into the cartilage and bone, encroaching and destroying them (2).

The cells contain proteolytic enzymes which enable them to enzymatically degrade cartilage and bone in short-term repeating episodes during the course of the disease. On the contrary, the immunological non-bacterial inflammation damages neither cartilage nor bones due to a complex inhibitory system.

Apart from immunological inflammation and oncological destroying process the seropositive RA is characterized by the formation of primary necroses, predominantly developing in cell-poor collagenous tissue. These necroses in RA (RAN) can occur in tendons, eyes, lungs, blood vessels as well as in the pericard, myocard and endocard. They represent a dangerous systemic complication, which can lead to death under certain circumstances.

Our analytic studies at 492 RAN of seropositive patients showed that the process begins with occurrence and proliferation of round cells with large nuclei, which in regard neither to phenotype nor to function can be counted among fibroblasts or other body cells (3). These cells secrete MMP-1 and thereby dissolve collagenous stroma leading to the formation of necrotic centre, which is surrounded like a palisade.

To sum up, the immunological inflammatory process shows up to be responsible only for the well-known pain symptomatology of RA. However, the intrinsic activity of the disease, i.e. the joint destruction and tissue necrotising, is obtained by autonomous, oncological proliferative mechanisms.

Autonomous oncological proliferation processes (OPP) in SSA

The SSA are characterized by bone mutilation and by fusion of neighboring articular bones leading to loss of the joint gap (4).

The resulting joint destruction is promoted by new formation of osteoblasts. Finally, proosteoblasts and osteoblasts develop from subperiosteal resting pluripotent fibroblasts. Underneath the periost of the corticalic substance they form a new, disordered, often bizarre looking fibrous bone. Construction and new ossification processes are caused, in the region of the spongiosa, which can reach the joint cavity and release a non-bacterial inflammation.

However, beyond that the bone processes can bridge the joint gap, get in touch with the neighboring articular bone and unite with it.

The pain symptomatology is released by friction of the periost as well as by synovitis. Mutilation and ankylosis, however, are the work of the described autonomous oncological proliferative processes.

In AS an analogous process courses at the vertebral column. It is also an autonomous oncological proliferative process with new formation of osteoblasts, ossification of the anulus fibrosus, osseous bridging of the intervertebral space and ankylosis of the vertebrae.

Like all autonomous oncological proliferative processes it is also accompanied by non-bacterial inflammations, whose symptoms, however, without meaning for the actual process; mask the basic mechanism.

The fact that in the pathological ossification inflammatory components do not play any role explains why substances, which intervene in any stage of the inflammation, cannot restrain the crucial process. Above all it is shown that all therapies set up to work at the improvement of the clinical symptomatology hit only the mantle, but not the core of the disease.

References

1. GAY S, HUANG G, ZIEGLER B, FASSBENDER HG, GAY RE. Expression of MYB, MYC, RAS, and FOS oncogenes in synovial cells of patients with rheumatoid arthritis (RA) or osteoarthritis (OA). Arthritis Rheum 1989;35:304-10.
2. FASSBENDER HG. Histomorphological basis of articular cartilage destruction in rheumatoid arthritis. Collagen Rel Res 1983;3:141-55.
3. ERNST N, MEYER-SCHOLTEN C, ZORN K, KRENN V, FASSBENDER HG. Entstehung und Entwicklung der RA-Nekrosen (rheumatoid nodules). Zeitschrift für Rheumatologie 2005;64:I/54.
4. FASSBENDER HG. Pathology and Pathobiology of Rheumatic Diseases. 2nd ed. Berlin: Springer, 2002:177ff.