Activated fibrocytes

Circulating cells that populate the arthritic synovium?

This editorial refers to ‘Fibrocyte activation in rheumatoid arthritis’, by Carole L. Galligan et al., doi:10.1093/rheumatology/kep265, on page 640.

In this issue of Rheumatology, Carole Galligan and co-authors [1] present a study that detects a specific cell population, fibrocytes, in the serum of patients with RA and in healthy controls. Fibrocytes are rare cells (1–2% of the leucocytes in healthy individuals) that share surface characteristics of both leucocytes and mesenchymal cells [2]. Previous studies show that fibrocytes can function as immune cells and also have properties of mesenchymal stem cells [3]. In addition, this study also shows that the fibrocytes in RA have an activated profile that detects different phosphorylated molecules in the mitogen activated protein kinase (MAPK), and signal transducers and activators of transcription (STAT) pathways. The total number of circulating fibrocytes, however, was not different between the control and RA groups. The data contribute to our understanding of the role of mesenchymal cells in the pathogenesis of RA.

In a joint affected by RA, the synovium undergoes dramatic changes. It transforms from a quiescent tissue with nutritional and homeostatic properties into an intense battleground with ongoing immune and inflammatory reactions, cell accumulation, proliferation and transformation, and has a key role in cartilage and bone destruction, leading to loss of joint function. The role of classic immune and inflammatory cells such as macrophages, T-, B- and dendritic cells have been studied extensively, and successful therapies that target these cells types or some of the key cytokines that they produce have been introduced over the past decade. In parallel, further research into the mesenchymal cell populations in the synovium, in particular, the so-called synovial fibroblast-like synovial cell (FLS) has led to new concepts in RA [4].

The FLS population is not only a major player in tissue destruction in RA but also contains cells that have in vitro and in vivo characteristics of mesenchymal stem cells capable of differentiating into cartilage, bone, fat or muscle [5]. In addition, one study highlighted the immune-modulating properties of mesenchymal (stem) cells [6]. The definition and characterization of the cell types in the mesenchymal population are still ongoing. FLS can be considered to be a group of cells; some of which have the characteristics of mesenchymal stem cells but others may not. Fibrocytes, found in peripheral blood, may migrate to the synovium and become part of the FLS population. The specific identification and isolation of these cells types from the synovium are still a major challenge.

Most attention has been paid to the role of FLS in pannus tissue, because effector cells produce tissue-destructive enzymes such as MMPs and stimulate the differentiation and activation of osteoclasts through the receptor of nuclear factor kappa B (RANK) system. The increased number of cells in pannus tissue contrasts with the relatively low number of mitotic cells in the tissue [7]. This observation stimulated Galligan et al. [1] to study the role of circulating fibroblast-like cells in RA and hypothesize that such a cell population can migrate into the RA synovium. Multi-colour flow cytometry is introduced as a method to adequately phenotype fibrocytes from peripheral blood, as these cells are rare and therefore complex to detect. Current flow cytometry approaches allow the concurrent detection of surface markers and intracellular markers. Moreover, detection of phosphorylated proteins also allows visualization of activated signalling pathways.

In an attempt to corroborate these findings in a more controlled setting, similar cells were detected with CIA, a well-known model of RA. In this model, an increase in activated fibrocytes was found in the early, pre-clinical disease stages. Of specific interest, cells with phenotypic characteristics of fibrocytes, both CD45-positive, a common leucocyte marker and z-smooth muscle actin-positive (aSMA), a marker for myofibroblasts, were found in affected joints of mice.

The authors propose that fibrocytes might contribute to the mesenchymal cell population in the arthritic synovium and thereby influence the disease process. Previous studies have suggested that circulating or migrating mesenchymal cells have a role in joint diseases [8, 9]. In particular, bone morphogenetic protein (BMP) receptor-positive cells originating from the bone marrow have been identified in patients with RA and in mice with CIA [8, 9]. Of interest, the migration of such cells from the bone marrow into the synovial tissue in CIA preceded the onset of clinical symptoms and the development of the hallmark histological features of the disease. Verschueren and colleagues [10] showed that BMP-responsive cells are found in different synovial compartments in RA patients and some of these cells are also aSMA positive. All these data provide experimental support for an evolving hypothesis about the different roles of mesenchymal cell populations in the joint.

Increasing evidence supports a key role for these cells in defining the stromal code, which interacts with immune cells in different ways. Specific cell types may be attracted to the synovium, whereas other signals may be responsible for retaining specific cell types [4]. Some of
these cells may act as signalling centres extending their regulatory roles into non-immune processes such as
angiogenesis and dedifferentiation. Mesenchymal stem cell populations have also been shown to display some
immunomodulating and even immunosuppressive properties. These functions may be changed in chronic arthritis
as supported by a reversal of the immunosuppressive properties by TNF in a mouse model [11].

All these concepts and data highlight the need for additional studies into the specific molecular characteristics
of the mesenchymal cell population in the synovium both in healthy individuals and in patients with RA. Indeed, not all mesenchymal populations are the same. Stem cells from the synovium have different properties as compared with bone marrow or perist and molecular profiling suggests a role for specific signalling pathways depending on the tissue of origin [12]. The heterogeneity of synovial cell populations has also been recently highlighted [13].

However, the study discussed in this editorial has some limitations. First, only a small number of patients were studied and, thus, their individual characteristics and disease processes may be different. However, it is a proof-of-principle study to set up additional and larger cohort studies that could be followed up prospectively or the analysis incorporated into clinical trials. Second, the analysis of the activation state of the fibrocytes is somewhat arbitrary and lacks specificity. The signalling effectors chosen in this study are likely candidates as indicators of activation in the fibrocytes, but this choice was also influenced by the availability of specific reagents at the time of the study. Third, it cannot be excluded that at least part of this activation profile is secondary to a more generalized inflammatory response in patients with RA. Last, the authors have not shown that activated fibroblasts migrate into the RA synovium, since fibrocytes in human beings seem to lose their dual characteristics after differentiation into a SMA-positive cells. CD45-aSMA double-positive cells were found in the synovium of mice with CIA. By contrast, the temporary increase in activated fibrocytes in this model is not in line with the persistent findings in the RA patients, which may be explained by clear differences and shortcomings of the experimental model that in essence is an immunization with cartilage antigens.

In conclusion, Carole Galligan and co-authors provide an interesting angle to a well-known problem. Hopefully, their study will further increase the interest and propel research into these cell populations with a better understanding of the stromal code.

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