Does epithelial-mesenchymal transition happen in rheumatoid joints?

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To the Editor,

The epithelial-mesenchymal transition (EMT), a cell biological process playing critical roles in early embryonic morphogenesis, can enhance the migration and invasion of tumor cells. In rheumatoid arthritis (RA), abnormal expansion of pannus tissue is a crucial feature responsible for disease progression, and pannus formation with highly proliferative synovial fibroblasts (SF) can cause bone erosion and cartilage destruction. The rapid progression of joint destruction in the relative absence of synovitis suggests the aggressive characteristics of RA synovium, resembling neoplastic tissue. Moreover, RASF, with morphological characteristics similar to transformed cells, could grow in vitro in an anchorage-independent manner, a property that correlates closely with tumorigenicity (1). Interestingly, in a severe combined immunodeficiency mouse co-implantation model, RASF maintained their invasive behaviors independently of T cells (2). However, the molecular mechanisms underlying their transformation characteristics remain largely unknown.

As early as 2006, one study described a regulated process resembling the EMT that was responsible for the altered phenotype of the synovial lining in RA. By immunostaining with E-cadherin (E-cad) and α-smooth muscle actin (α-SMA) antibodies in the synovial tissue of healthy individuals and RA patients, they proposed that healthy SF might undergo a process comparable to the EMT under the stimulus of transforming growth factor-β (TGF-β) in the synovial fluid from RA patients (3). A recent report also confirmed the finding by showing that hypoxia-induced EMT was accompanied by increased migratory and invasive phenotypes in RASF (4). The concepts of these two studies raised controversy by the fact that synovial lining lacks a basement membrane and should not express E-cad. Another critical point is that SF are already mesenchymal cells and should not undergo EMT or a regulated process resembling EMT. How the two studies achieved this conclusion should be further reconsidered unless these critical points can be solved.

Various factors responsible for the EMT process are found in rheumatoid joints. Abundant amounts of TGF-β are present in the synovial fluid of RA patients (5). SLUG, a zinc-finger transcription factor family member, was identified in the synovial tissue of RA patients and correlated with the invasive phenotype of RASF (6). Increased expression of α-smooth muscle actin (α-SMA) in high-inflammation synovium of RA patients suggests a clear presence of this molecule on fibroblast-like synoviocytes in the lining layer (7). Although these facts clearly indicate a potential role of EMT in rheumatoid synovium, several reservations should be made, because very few cells express epithelial features; classical E-cad is scant due to the synovial lining lacking a basement membrane; and fibroblasts are mesenchymal cells that should not undergo EMT. These critical points need to be solved to clearly identify the role of EMT in rheumatoid joints.

Because of the resemblance to neoplasia, the EMT will be an attractive mechanism to explain the invasive phenotype of RASF, although it remains a puzzle to complete. The origins of cells that are responsible for this converting process should be further clarified. We suspect more detailed mechanisms can be proposed to explain the role of the EMT in rheumatoid joints in the future.

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References


