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RA synoviocytes induce T cell anergy

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CD80, synovial fibroblasts, T cell anergy

Context

Fibroblast-like synoviocytes (FLSs) in the rheumatoid synovial membrane (RA SM) show an activated phenotype with increased expression of MHC class II and adhesion molecules. It has been suggested that FLSs act as antigen presenting cells, and are involved in the activation of T cells. Within the RA SM, FLSs do not express CD80 or CD86 (B71 and B72), the classic ligands for CD28 and CTLA-4. Antigen presentation to T cells in the absence of a second signal may lead to T cell anergy, characterised by arrest at the G1 stage of the cell cycle with expression of the interleukin (IL)-2-receptor β chain CD25, but failure to produce IL-2. It has been shown that keratinocytes expressing MHC class II can induce short term anergy in this way (see Additional information). The authors investigated whether T cells within the RA SM are anergised by contact with FLSs. Specifically the authors investigated the phenotypic changes in FLSs and T cells co-cultured in either an autologous or an allogeneic *in vitro* system. They studied the functional effect of FLSs on T cells in the presence/absence of CD80, and tested whether primary contact with antigen presented by FLSs in the absence of CD80 costimulation induced T cell anergy.

Significant findings

Co-cultures of peripheral blood (PB) T cells with FLSs showed that activation markers are upregulated on both T cells (CD69, CD25) and FLSs (HLA-DR). Both PB T cells and RA synovial T cells showed reduced responses to allogeneic or recall antigen when co-cultured with FLSs. This reduced response could be normalised by including CD80-transfected fibroblasts in the co-cultures, indicating a role for CD80 in this system. Preculturing T cells with FLSs induced nonresponsiveness ('anergy') in both PB and RA synovial T cells tested in a two-stage culture protocol. Such nonresponsive T cells had three features suggestive of anergy: they failed to proliferate in secondary culture even in the presence of CD80, CD25 expression increased and proliferation could be restored by the addition of recombinant human IL-2.

Comments

FLSs are known to play a role in the pathogenesis of RA, as a component of erosive pannus and through driving B cell activation and rheumatoid factor production. When T cells enter the synovium they may interact with activated FLSs on a cell-to-cell basis in the absence of nominal antigen. There has been some speculation on a role for FLSs' interaction with T cells; contrasting studies suggest that they may either activate or induce anergy in T cells. The authors attempted to replicate this FLS-T cell interaction *in vitro* using both an autologous and an allogeneic co-culture system. Their results support the view that FLSs induce T cell anergy. The authors speculate that such anergy is a means of preventing T cells from being inappropriately stimulated by activated MHC-class-II-positive FLSs that could act as potential antigen presenting cells during inflammation. This represents an interesting observation, particularly given the known hyporesponsiveness of RA T cells and their high expression of CD69. This *in vitro* system is limited, however, in that it cannot fully reproduce the synovial environment. Thus, as the authors discuss, abundant CD86 on bystander cells in the RA synovium may provide sufficient costimulation for the FLS to induce activation rather than T cell anergy *in vivo*.

Methods

In vitro co-culture and proliferation assays, FACS analysis, peripheral blood T cells, fibroblast-like synoviocytes

Additional information

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Alloantigen-specific T-cell anergy induced by human keratinocytes is abrogated upon loss of cell-cell contact. *Immunology* 1996, **88**: 214-219.

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