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FIBROBLASTS FROM DIFFERENT TISSUES PROMOTE ENTRY BUT RETAIN LYMPHOCYTES IN 3D MODELS OF TISSUE.

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Background and objectives Fibroblasts actively regulate the recruitment of leucocytes by endothelial cells, acting in a pro- or anti-inflammatory manner depending on their site of origin.¹ Effects of fibroblasts on leucocyte migration through tissue and their subsequent fate remain unclear. Here, the authors explored the concept that fibroblasts from different tissues modulate the migration patterns of peripheral blood lymphocyte (PBL) in a site specific manner.

Materials and methods Fibroblasts were isolated from the skin, bone marrow and synovium of patients with rheumatoid arthritis (RA) undergoing joint replacement surgery. Two forms of co-cultures were developed, appropriate to answer specific questions: (1) endothelial cells and fibroblasts cultured on separate 3.0 µm porous filters, one above the other; (2) endothelial monolayers formed on a filter above a collagen gel in which fibroblasts were incorporated. In the multi-filter model, PBL adhesion and migration was assessed at 24 h by flow cytometry. In the collagen construct, PBL migration into the gel and their depth of penetration was assessed at intervals over 48 h.

Results The authors used the multi-filter model to assess the ability of fibroblasts to influence PBL migration through resting endothelial monolayers. Fibroblasts, synovial and dermal, enhanced the ability of endothelial cells to support T cell adhesion, and significantly promoted their onward transendothelial migration. Although fibroblasts generate CXCL12 and IL-6, blockade of either protein had no effect on T cell migration. Interestingly, fibroblasts appeared to restrain onward motion of recruited T cells. This indicated that the process of migration changed the migratory phenotype of recruited T cells and/or that fibroblasts were providing 'stop' signals resulting in T cell retention within the fibroblast layer. Next, the authors employed the multi-cellular collagen gel construct to visually observe the effects of fibroblasts on PBL migration into and retention within tissue. Once again, all fibroblast types promoted PBL transendothelial migration, while reducing their onward penetration of the collagen gel. Notably, migrating PBL tracked closely to fibroblast rich regions of the gel, indicating that fibroblasts are capable of retaining recruited cells.

Conclusions Collectively these data suggest a novel regulated step in lymphocyte migration, where stromal-derived 'go' and 'stop' signals control lymphocyte migration into and within tissues, respectively.

REFERENCE

1. McGettrick HM, Smith E, Filer A, *et al.* Fibroblasts from different sites may promote or inhibit recruitment of flowing lymphocytes by endothelial cells. *Eur J Immunol.* 2009;**39**:113–25.