Regulation of signaling through the fibrocytes: novel, circulating fibroblast-leucocyte/stromal cell interactions in inflammation

Several chronic systemic diseases are characterised by inflammation which can affect different tissue organs simultaneously. Phenotypic analysis of the lymphocyte infiltrate, typically found at sites of chronic inflammation, indicates that distinct subsets of lymphocytes accumulate in different tissues such as lung, gut, skin and joint. The role for these cells is not completely understood but it is thought that regulatory mechanisms intervene at least at three different levels. The first level of control relates to specific lymphocyte-endothelial recognition systems operating in the microvascular beds of various tissues. These include the interaction of lymphocyte "homing" receptors such as L-selectin, CLA and 447 with the respective endothelial "address" ligands PNA, E-selectin and MADCAM-1. A second level of regulation may involve the local production of specific chemokine receptors capable of recruiting lymphocytes programmed to recirculate to a given tissue. Although further work is needed in this area it appears that some chemokines can act on distinct subpopulations of lymphocytes. Finally, once in the tissues, specific lymphocytes can be preferentially retained locally by binding to selective tissue ligands. An example of this is represented by 447 positive lymphocytes which bind gut epithelial E-cadherin. Such complex regulation of lymphocytes migration will allow specific homing to exist along side universal migration. This will facilitate the development of immune responses in specialized compartments while permitting their integration throughout the body.

Role of LFA-1/ICAM adhesion in leucocyte/stromal cell interaction

The leucocyte integrin LFA-1 (CD11a/CD18) is a cell surface receptor which mediates adhesive interactions and signal transduction in the immune system by binding its ligands ICAM-1, -2 or -3 expressed by stromal cells. The l domain located on the α chain (CD11a) of LFA-1 (CD11a/CD18), plays an essential role in lymphocyte/endothelial cell adhesion. We have identified a new site in the l domain that is involved in ICAM-3 binding. A synthetic peptide containing the ICAM-3 binding site inhibited ICAM-3 dependent adhesion and proliferation of resting T cells, suggesting that this peptide interferes with immune recognition, and can be used as immunosuppressive agents.

Regulation of signaling through the B lymphocyte antigen receptor complex

We recently described a population of novel, circulating cells that rapidly enter sites of tissue injury, synthesize connective tissue matrix, and can be localized to sites of fibrosis and scar formation (Mol Med Today; 4:171-81). These cells constitute 0.03-0.3% of blood-borne leucocytes and display a distinct cell surface phenotype (collagen/Cd13/CD45/esterase/cytokeratin/von Willebrand factor/α-actin). CD13+ /CD45+ /CD34+/CD11c+/CD14- /CD33+/CD15- cells preferentially retained locally by binding to selective tissue ligands. An example of this is represented by 447 positive lymphocytes which bind gut epithelial E-cadherin. Such complex regulation of lymphocytes migration will allow specific homing to exist along side universal migration. This will facilitate the development of immune responses in specialized compartments while permitting their integration throughout the body.