Regulation of endothelial recruitment of leukocytes by the local environment

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In inflammation, endothelial cells (EC) respond to cytokines and regulate recruitment of leukocytes through changes in expression of adhesion molecules and activatory signals. However, the responses of the EC themselves depend on local environmental factors, notably the circulatory shear stress and underlying stroma. Both vary between regions of the circulation and in disease. Increasing steady laminar shear stress progressively down-regulates the response to inflammatory stimuli. Thus, we found that conditioning EC by shear stress suppressed their recruitment of leukocytes in response to cytokines. In studies of stromal cells, co-culture of EC with fibroblasts or with mesenchymal stems cells (which are endogenous in tissues in small numbers), again down-regulated leukocyte recruitment. Such homeostatic regulation of the inflammatory response is disturbed in disease. Exposure to disturbed, oscillatory flow predisposes to the formation of atheroma at bifurcations in arteries. Indeed, oscillatory shear or sudden changes in shear may directly induce leukocyte adhesion. Disturbance of normal stroma, that occurs e.g., in rheumatoid arthritis or upon differentiation of MSC, leads to loss of protective effect or even a direct pro-inflammatory milieu. Thus, local environmental factors act as endogenous limiters of the inflammatory response. Their disturbance may be pathogenic, and understanding of the mechanisms may yield approaches to prevent or reverse chronic inflammation.