Inflammatory diseases

Endothelial cell heterogeneity determines neutrophil transmigration hotspots and limits vascular leakage

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The endothelial monolayer of the vasculature is a highly dynamic cell layer that controls on one hand the extravasation of leukocytes during inflammation and immune surveillance, while on the other hand limiting vascular leakage. Extravasation of leukocytes, or transendothelial migration (TEM), has been observed to occur at non-random sites in the endothelial monolayer, but the exact cellular and molecular mechanisms that allow this preferential transmigration are not completely understood. Here, we show that transmigration hotspots exist *in vitro* and show that neutrophils undergo more efficient TEM at these sites. We show that adhesion molecules ICAM-1, ICAM-2 and VCAM-1 are expressed in different degrees of heterogeneity in the endothelial monolayer and correlate transmigration hotspots with regions of ICAM-1 and ICAM-2, but not VCAM-1 high expressing endothelial cells. ICAM-1 and ICAM-2 are shown to be required in different steps of the TEM cascade, both being essential for the existence of transmigration hotspots. By removing heterogeneity in the monolayer, we observe increased leakage during TEM, suggesting that endothelial TEM hotspots are crucial in maintaining the vascular barrier integrity during inflammation.