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Talk Title: Lymphatic endothelial cells undergo directional migration in response to spatial gradients in wall shear stress
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Vinay N. Surya, Maggie A. Ostrowski, Eva Huang, Gerald G. Fuller, and Alexander R. Dunn

Endothelial cells (ECs) line the inner surface of blood and lymphatic vessels and are highly sensitive to fluid flow as part of their physiological function. EC organization, migration and vessel development are profoundly influenced by hydrodynamic stresses, with important implications in cardiovascular disease and tumor metastasis. How ECs sense fluid flow is a central and unanswered question in cardiovascular biology.

We developed a high-throughput live-cell fluid flow chamber which models the gradients in wall shear stress experienced by ECs in vivo. Live-cell, time-lapse imaging allows us to probe important cellular responses to flow, most notably EC migration, which has a key role in vessel remodeling (Figure 1). We find that most EC subtypes, including ECs from the venous, arterial, and microvascular systems, migrate in the flow direction. In contrast, human lymphatic microvascular ECs (hLMVECs) migrate against flow and up spatial gradients in wall shear stress, a behavior we term rheotaxis. Further experiments reveal that hLMVECs are sensitive to the magnitude, direction, and the local spatial gradient in wall shear stress. A screen of canonical cellular signal transduction pathways reveals that the membrane-bound G-protein coupled receptor (GPCR) sphingosine 1-phosphate receptor 1 (S1PR1) is required for directed, flow-induced migration in hLMVECs.

Based on these data we developed a linear response model that predicts EC polarization and migration in response to wall shear stress. We suggest that the migration of lymphatic ECs up spatial gradients in wall shear stress may play a role in lymphangiogenic remodeling, in which lymphatic vessels grow towards and drain tissues with high interstitial fluid pressure.

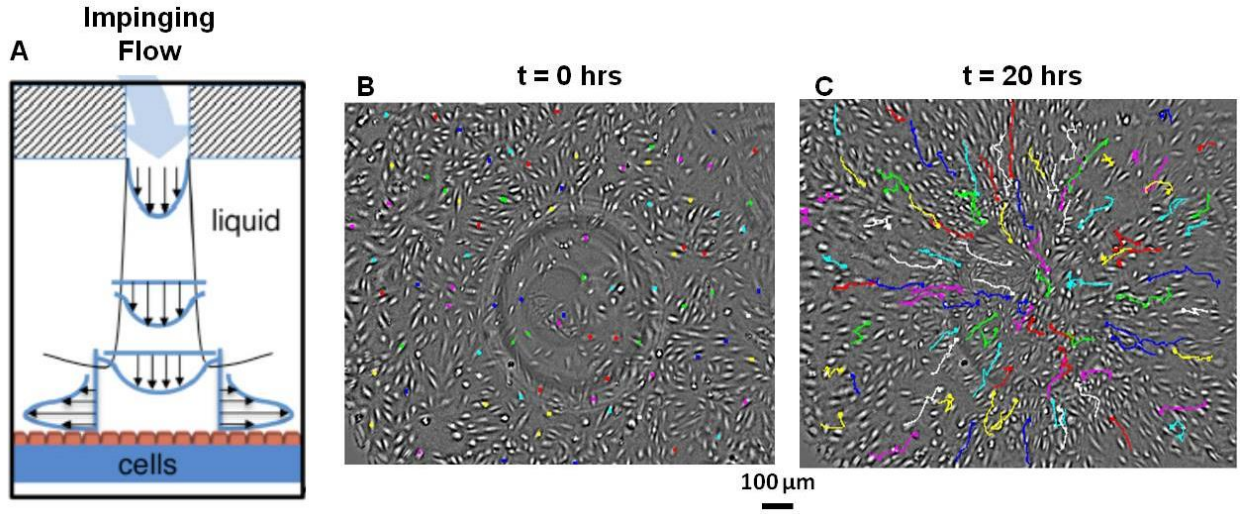


Figure 1. (A) Schematic of the fluid flow chamber. ECs (orange) are seeded on a gelatin-coated coverslip (blue) and are exposed to an impinging flow that generates spatial gradients in wall shear stress. (B) Live-cell imaging allows us to visualize EC migration in response to flow. The gray ring is the shadow of the jet apparatus, and shows the inner jet radius. Individual cells are marked with colored dots. Flow impinges vertically in the center of the image and spreads radially outward, creating a maximum in wall shear stress 400 microns from the jet center. Wall shear stress decays to negligible levels at large distances from the jet. (C) hLMVECs migrate inward toward the jet center, up the local gradient in wall shear stress and against the direction of flow. Individual cell trajectories are indicated by colored lines, with the end point shown as a dot.