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Excess Interstitial Fluid of Lymphatic System Drains

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Description

The lymphatic system drains excess interstitial fluid and returns it to the circulating blood. Improper lymph drainage due to either vessel malformation or valve malfunction can lead to tissue swelling, termed lymphedema, which in addition to disfigurement and debilitation can contribute to the pathophysiology of atherosclerosis, hypertension and the formation of blood clots (thrombosis). Failure to establish proper cardiac lymph drainage is also thought to be a primary factor in organ rejection for heart transplants, further illustrating the importance of this sometimes overlooked component of the circulatory system.

The 6-well IFC apparatus fits on standard 6-well cell culture plates, applies an axisymmetric WSS gradient about the flow-stagnation point, and is compatible with both bright field and fluorescence live-cell imaging. Advantages of the IFC are that it applies a range of WSSs in one experiment, and moreover replicates the spatially varying WSS found at vessel bends, constrictions and bifurcations. The magnitude of the maximum WSS and WSS gradient can be tuned across a wide range of values by changing the flow rate. In previous work, we assayed a number of adherent cell types and found that, unusually, HLMVECs migrate upstream, against the direction of flow. This upstream migration required cell-cell contact, as cells without nearby neighbours were unable to migrate against the flow direction, indicating that the migratory response was a collective rather than individual response to WSS.

Importance of Fluid Flow

Fluid flow is an important cue in the development and stabilization of the lymphatic system. Lymphatic Endothelial Cells (LECs), which line lymphatic vessels, experience a wide range in Wall Shear Stress (WSS), ranging from 0 to 12 dynes cm−2 in rat mesenteric prenodal lymphatics [13], and up to 40 dynes cm−2 in models of lymphedema. Interestingly, the physical cue provided by WSS has been proposed to play an essential role in the development of lymphatic valves, which preferentially form at constrictions and vessel junctions, where both geometries feature spatial gradients in WSS.

Previous studies have examined how endothelial cells (ECs) from the blood vasculature sense and respond to fluid flow. PECAM-1, VE-Cadherin, VEGFR-2 and VEGFR-3 have previously been identified as components of a molecular flow sensor that converts the physical stimulus provided by WSS into downstream signalling via VEGFR and PI3K. G-protein-coupled receptors (GPCRs) have also been implicated in flow sensing. Notably, measurements using a Förster resonance energy transfer-based sensor suggest that bradykinin B2 undergoes changes in conformation and activity in response to fluid shear stress, consistent with a direct role in flow sensing. Recent evidence likewise implicates sphingosine 1-phosphate receptor 1 (S1PR1), another GPCR, in the response of endothelial cells to fluid flow. S1PR1 knockout mice die in utero between E13.5 and E14.5 due to defects in vascular stabilization. How S1PR1 contributes to vessel stabilization is incompletely understood. However, previous work shows that the presence of S1PR1 was required for human umbilical vein ECs (HUVECs) to initiate downstream signalling via ERK1/2 specifically in response to WSS.

Before exposing the cells to impinging flow, the IFC was prepared by adding 10 ml of L-15 medium to each of the six chambers in the absence of cells followed by the removal of bubbles. Medium was circulated through the device tubing. Once the tubing lines were filled, the device was stopped and the remaining air was removed through a syringe. The flow rate in all experiments was 1.5 ml min−1, corresponding to a peak WSS of 9 dynes cm−2. All flow experiments were performed for 20 h. Cleaning of the device after each experiment was performed analogously to preparation and is detailed in our prior publication. Parallel plate experiments were performed using the same peristaltic pump detailed above. Shear stress calculations for the channels used were provided online by Ibidi. All parallel plate experiments were performed with a uniform WSS of 12 dynes cm−2 corresponding to a flow rate of 7.3 ml min−1

Migration of Cell

Cell migration was captured through a Flea 3 camera using a Nikon TE inverted microscope (Nikon Corporation, Tokyo, Japan) with a Nikon 4× objective and a 1.5× tube lens. A custom designed temperature control chamber was used to keep the ambient temperature at 37°C.

More broadly, S1PR1 and its ligand S1P are known to play central roles in individual and collective cell migration. The concentration of S1P is negligible in interstitial fluid, but is ca. 100 nM in blood and lymphatic fluid. Because of this, the local concentration of S1P provides an important cue in the context of immunological function, lymph angiogenesis and blood vessel stabilization. Loss of S1PR1 in RBL-2H3 cells, derived from mast cells (a type of white blood cell), results in decreased chemotactic motility, and S1PR1 activation via S1P is required for lymphocyte egress from the thymus and secondary lymphoid organs in mice. S1P promotes LEC sprouting in vitro in a manner that requires S1PR1. In zebrafish embryos, S1P and its receptors are required for collective migration of prechordal plate progenitor cells. This observation suggests that signalling via S1P may play broader roles in embryonic development than is currently appreciated.

Previously, we developed an Impinging Flow Chamber (IFC) to impart controlled spatial gradients in WSS to a monolayer of adherent cells in a six-well plate fashion. Using this device, we found that human lymphatic microvascular endothelial cells (HLMVECs), uniquely among the cells assayed, migrated upstream, against the flow direction. Here, we show that this upstream migratory phenotype requires both S1PR1 and its ligand S1P. As discussed above, the requirement for S1P is significant in that S1P provides a chemical cue unique to the lymphatic and blood circulatory systems. Our data are consistent with a model in which S1P and flow act synergistically during the development and remodelling of the lymphatic system.