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Micro-vascular systems on a chip

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Cellular and molecular interactions are critical to many physiological, pathological and pharmacological processes in the microvasculature. For instance, they play an important role in determining the delivery performance of therapeutics transport *in vivo*. Static well plate assays and in vitro fluidic devices have been instrumental in our understanding of the biological interactions. However, widely used flow chambers suffer from several limitations for studying the *in vivo* microvascular environment. These include (a) lack of critical morphological features (e.g., bifurcations, tortuosity), (b) inability to distinguish between healthy vs. diseased vasculature, (c) large consumable volumes, and (d) inability to support co-cultures. To overcome these limitations, we have developed SynVivo (derived from 'synthetic *in vivo*') microfluidic assays for studying cell-cell and cell-drug studies in an *in vivo* like environment. The SynVivo devices are based on idealized and *in vivo* derived microvascular networks patterned onto a plastic, disposable substrate to mimic the morphological and physiological conditions observed *in vivo*. The devices can be functionalized using a variety of cells (e.g., endothelial, tissue, tumor) and combine two critical elements characteristic of the *in vivo* micro-vascular milieu: (a) 3D multi-cellular cultures to capture the realism, and (b) fluid shear and mechanical strain to capture the dynamics, thereby affording high-fidelity simulation of cell, tissue or organ physiology. Sample results from case studies on drug particle adhesion, drug transport, particle shape effects, gene delivery, cell migration and toxicity will be presented. Future applications of the platform will be discussed.

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Molecular mechanism and prevention of VEGF-induced micro-vascular leakage in the retina of diabetic mice

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Diabetic retinopathy is predominantly caused by vascular endothelial growth factor (VEGF)-induced micro-vascular leakage; however, the underlying mechanism is unclear. Here, we demonstrated that hyperglycemia induced micro-vascular leakage by activating TGase2 and this vascular leakage was inhibited by C-peptide in diabetic retina. VEGF elevated TGase2 activity through sequential elevation of intracellular $Ca2^{+}$ and reactive oxygen species (ROS) levels in endothelial cells. The TGase inhibitors cystamine and monodancylcadaverin or TGase2 siRNA prevented VEGF-induced stress fiber formation and vascular endothelial (VE)-cadherin disruption, which play a critical role in modulating endothelial permeability. C-peptide inhibited the VEGF-induced ROS generation, stress fiber formation and disassembly of vascular endothelial cadherin in endothelial cells. Intra-vitreal injection of C-peptide, two TGase inhibitors, or TGase2 siRNA successfully inhibited hyperglycemia-induced TGase activation and micro-vascular leakage in the retinas of diabetic mice. Thus, our findings suggest that C-peptide prevents VEGF-induced micro-vascular permeability by inhibiting ROS-mediated activation of TG2 in diabetic mice.

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