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Profiling Nitric Oxide metabolites in endothelial dysfunction using 3D blood vessel model

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Endothelial dysfunction is the prime cause of many pathological conditions such as atherosclerosis, thrombosis, platelet aggregation, inflammation, and defective oxygen mechanism due to hypoxic conditions. The natural mechanism in maintaining vascular endothelium involves various signaling compounds and mechanistic factors such as fluid flow and shear stress. Among all signaling compounds, Nitric Oxide (NO) is considered an essential one in maintaining vascular homeostasis. Hence, analysis of the NO level is necessary for understanding pathological conditions. Evaluating the level of NO to predict the risk of endothelial rupture is crucial for patient management, yet current two-dimensional endothelial cell culture models and methods suffer from several limitations due to NO's short half-life and lack of fluid flow in the model. This results in less NO expression and displays a non-physiologic phenotype.
This study focuses to compare two-dimensional (2D) and three-dimensional (3D) platforms in terms of NO-specific metabolites level. To measure NO metabolites using UPHPLC/MS in a three-dimensional model, we developed a tracer-based metabolomics strategy in the three-dimensional micro vessels-on-a-chip model with a microfluidic pump, that maintains a unidirectional fluid flow. And we investigated the specific marker isotope metabolites, tracking through the NO substrate L-Arginine in the NO mechanism. We detected significant changes in L-citrulline and L-ornithine levels in stimulation and inhibition of the eNOS (endothelial nitric oxide synthase) enzyme. Compare to the 2D culture, the augmented effects of NO specific metabolite, L-citrulline was determined in 3D blood vessels. We also studied the impact of oxygen in endothelial dysfunction condition over NO metabolism with an in-line oxygen measurement system. This model signifies a more similar physiological environment that displays the difference between 2D and 3D cultures.

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