Microphysiological systems for modelling microvasculature and multicellular-vascular interactions using microfluidic technology

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The recent application of microfluidic technologies in bioengineering has driven considerable progress in the design of 3D tissues on chips, which offer the possibility to improve preclinical experimentation with respect to traditional 2D culture systems, in agreement with the 3Rs principle. Commonly referred to as microphysiological systems, such biomimetic *in vitro* models replicate the *in vivo* tissue-specific microenvironments making use of human induced pluripotent stem cells (iPS) or primary cells embedded in extracellular matrix (ECM)-like hydrogel.

Here, we introduce the design of bio-inspired 3D microphysiological models of the human Blood-Brain barrier, KRAS/LKB1 lung tumor microenvironment and ALK-positive Anaplastic Large Cell Lymphoma (ALCL) as models of multicellular-vascular interactions in a microfluidic device. These models have in common an advanced perfusable microvasculature, developed by different strategies, self-assembled vasculogenesis, or cell culture in 3D macrovessel, and supported by cell-cell dynamic contact interactions and continuous secretion of signaling factors. The BBB model, which used iPS-derived cells, showed increased maturation toward BBB-like structures with vascular permeability lower than conventional *in vitro* systems, and it was used to test transport of innovative carriers, such as polymer nanoparticles. With the advent of immunotherapies, the lung tumor-microvascular model was critical to understand the biology of immune cell recruitment and exclusion to the lung microenvironment. The ALCL model was exploited to unveil a molecular mechanism of tumor drug resistance. These robust and physiologically-relevant models have the potential to revolutionize prognosis and therapy, predict more reliable therapeutic vulnerabilities and study the transport of drugs across barriers, thereby accelerating drug discovery, and improving understanding of several currently incurable diseases.