MODELLING T CELL MIGRATION IN 3D VASCULAR BEDS

DSP216 BLOCKS HLA-G AND CD47 SIGNALING

Recent clinical success of immune checkpoint inhibitors and chimeric antigen receptor T cells has highly increased the attention for the field of immunotherapy. However, identifying responders to these therapies is challenging underscoring the necessity for translational models that increase understanding of tumor-immune responses.

Materials and Methods In the present study, a co-culture system containing immune cells and vasculature was established. Both are essential components of the tumor microenvironment and very often lacking in *in vitro* tumor models, highlighting the added value of our co-culture platform. We focused on optimizing endothelial and CD8+ T cell co-cultures and subsequently assessing T cell migration from the endothelial tubes via endothelial sprouts towards various chemo attractants. In order to generate stratified 3D co-cultures, the Mimetas OrganoPlate Graft containing 64 microfluidic culture units was used. The microfluidic units in this platform are composed of two parallel microfluidics channels and a central chamber. The two parallel microfluidic channels were used for generating parallel endothelial tubules, whilst angiogenic factors (SIP, VEGF, bFGF and PMA) were added to the central chamber of the culture unit resulting in a generation of a gradient and sprouting of the endothelial tubes towards the central chamber. Generated sprouts were stable and perfusable. The central chamber is designed for culturing complex microtissues such as spheroids, organoids and explants.

Results Angiogenic endothelial tubules formed vascular beds in presence of added factors within 3–5 days. Once vascular beds were formed, activated and fluorescently labeled CD8+ T cells were loaded in the endothelial tubules and followed in culture for 48 hours. CD8+ T cell migration was observed both via the sprouts as well as by crossing the endothelial barrier, and increased in presence of gradients of CCL2, CCL112 and CCL9. Highest CD8+ T cell numbers were observed in presence of a gradient generated with a mix of these three chemokines.

Conclusions Therefore, we present a high throughput co-culture system containing angiogenic endothelial tubules and CD8+ T cells. These co-cultures are highly suitable for studying T cell migration, event which precedes the detection and recognition of antigens at the surface of antigen-presenting cells and for interactions with other cells involved in the immune response. In addition, these co-cultures serve as a platform for understanding the interplay between T cell migration and angiogenesis in the tumor microenvironment. Furthermore, we envision that this model will evolve into an immunocompetent patient-derived tumor microenvironment that can be used to study immune responses to tumors.

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