Engineering human brain organoids with hPSC-derived microglia to study neurodevelopment and disease

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The human brain is unique in size and complexity, but also the source of some of the most devastating human diseases. While many neurological disorders have been studied in model organisms, recent studies have highlighted the existence of unique features of the human brain that cannot be easily modelled in animals. Therefore, stem cells-derived human brain organoids that recapitulate cell composition and tissue architecture of the human developing brain [1] are increasingly appreciated as complementary systems to mouse models for the study of brain development and neurological diseases. Furthermore, brain organoids are emerging as *in vitro* platforms for the functionally study of viral pathogenesis in a human context and in a physiologically relevant environment, as demonstrated for Herpes simplex and Zika viruses [2]. Despite that, state-of-the-art brain organoids do not generate the resident immune cells of the brain, the microglia, important players of neurodevelopment and pathology [3]. Thus, the presence of microglia in organoid systems would allow not only to more accurately model neuroimmune responses but also mechanistically explore the emerging contribution of microglia to neurodevelopmental disorders. In our lab, we are studying the role of microglia in the onset of Autism Spectrum Disorders (ASD). Our analyses reveal that among all brain cell types that populate the developing brain, microglia express the highest number of ASD risk genes. Therefore, we are focusing on the generation of brain organoids enriched with stem-cell derived microglia carrying ASD risk gene variants to precisely link defined genetic alterations and neurodevelopmental phenotypes.

References

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