Combining CRISPR-Cas9 editing with a novel 3D neuro-immune organoid model to explore the roots of neurodevelopmental disorders

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Abstract:
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 are increasingly appreciated as complementary systems to mouse models for the study of brain development and neurological diseases.

Despite that, state-of-the-art brain organoids do not generate the microglia, the resident and most abundant immune cells of the brain that play key roles in neurodevelopment and pathology. Notably, we find that 30% of risk genes for autism spectrum disorder (ASD) are expressed in human embryonic and fetal microglia, thus implicating possible alterations in microglia development and/or early function in the pathogenesis of ASD. Organoid systems that recapitulate early steps of microglia development and functionality represent valuable platforms to mechanistically explore the emerging contribution of microglia to neurodevelopmental disorders.

Here, we will present our strategy to establish a fully in vitro generated human neuroimmune organoid model by engrafting human stem cells-derived microglia progenitors into brain organoids. This 3D *in vitro* model offers great control over the process of microglia development and enables to selectively target the immune and/or neuronal cells through the innovative CRISPR-Cas9 system. As such, this integrated approach provides the highest level of disease modelling precision and ease of use, thereby allowing us to investigate the molecular mechanisms associated with individual ASD risk genes and to explore the cell type specific contributions in the onset of the pathology. More broadly, this in vitro platform can be applied to the study of a variety of brain disorders and will help illuminate the disease-relevant mechanisms of neuroimmune dysfunction.