Retinal organoids: a window into our eyes during development and disease

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Blindness poses a growing global challenge, with approximately 26% of cases attributed to degenerative retinal diseases. While gene therapy, optogenetic tools, photosensitive switches, and retinal prostheses offer hope for vision restoration, these high-cost therapies will benefit few patients. Understanding retinal diseases is therefore key to advance effective treatments, requiring *in vitro* models replicating pathology and allowing quantitative assessments for drug discovery. The key to increasing our understanding of outer retinal disease mechanisms is the establishment of *in vitro* experimental models of the human retina that replicate disease pathology and permit the quantitative assessment of parameters for drug discovery. Relying solely on experimental animals is no longer sufficient, as differences in physiology and disease mechanisms often exist between these and humans. Pluripotent stem cells (PSCs) offer great promise in this respect. The ground-breaking study by Sasai and colleagues in 2011 demonstrated the replication of retinal development in three-dimensional (3D) culture conditions using murine embryonic stem cells (ESCs) [1, 2]. Subsequently, this achievement was replicated using human ESCs and induced pluripotent stem cells (iPSCs) and the resulting cellular organisations are now routinely referred to as retinal organoids - 3D laminated structures comprising all essential retinal cell types, faithfully recapitulating retinal development and function, including interconnected and light-sensitive photoreceptors [3]. The capacity for self-assembly of a stratified replica of the retina is of enormous value as this allows us to interrogate cellular interconnectedness – an aspect impossible with isolated retinal cells. This proves particularly valuable for assessing the impact of candidate drugs on the overall retina, so there is considerable excitement about the potential utility of retinal organoids for this purpose. However, it is crucial to acknowledge the artificial nature of these constructs, marked by several limitations, notably the absence of vascular input and immune system influence. While limited types of immune cells can be introduced, currently restricted to microglia, incorporating an RPE layer and integrating replicas of Bruch's membrane (BrM) and the choroidal vasculature demand further study. In this talk I will discuss the progress achieved in the last two decades concerning the differentiation of human PSCs into retinal organoids, focusing on their applications in disease modelling for age-related and inherited retinal diseases, the evaluation of new therapies, as well as contributions to drug repurposing, biomarker discovery, and toxicity assessment.

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