Müller glia in Retinal Disease and Regeneration (498 word presentation summary).

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With the 962million people over 60 is expected to double by 2050 (United Nations 2017) and the 488million diabetics expected to double by 2030 (WHO 2016) the global population is getting older and increasingly diabetic. As aging is strongly associated with the neural retina separating from the retinal pigment epithelium known as retinal detachment (Chang et al., 1995, Mitry et al., 2009, Van de Put et al., 2012). Plus, the hyperglycaemia from diabetes causes Müller Glia (MG) and capillary cell death, resulting in diabetic retinopathy, the leading cause of vision loss among working-age adults (Zong et al., 2010, Lee et al., 2015, Zeng et al., 2016) retinal degeneration is increasing. But MG are being researched as they show latent stem cell properties so could drive human retinal regeneration (Fischer and Reh 2001).

MG span the retina from the inner to the outer limiting membranes providing structural, homeostatic and metabolic support of retinal neurons (Reichenbach and Bringmann, 2013). But how MG arise is an active area of research, retinal differentiation is stimulated by a wave of Sonic Hedgehog (Shh) (Jarman, 2000) and MG are the last of the 7 specialised retina cell types to arise from retinal progenitor cells with Zeb2, Hes5 and Sox9 transcription factors involvement (Xiang 2012, Wei, et al. 2019). The determination of cell fate is not entirely understood with 3 proposed models, with each losing pluripotency in mammals with time (Reese 2011, He et al., 2012, Lamb, 2013). However cold-blooded animals such as zebrafish MG can maintain this pluripotency giving rise to all types of retinal neurons without injury trigger but for warm-blooded mammals injury is required (Goldman 2014).

Gliosis is the term used for this process of MG reacting to retinal damage, where damaged cells releasing ADP, TNF-alpha, Wnts and growth factors (GF) cause MG to prevent tissue damage by releasing antioxidants and neurotrophic factors. While microglia promote apoptosis through cytokines and the removal of neurons via phagocytosis (Silverman and Wong, 2018), in mammals gliosis ends with the formation of a glial scar that inhibits regeneration. However, in zebrafish GF, Wnt and cytokine signals cause MG reprogramming resulting in the following steps; (1) MG de-differentiation into retinal progenitors, (2) proliferation, (3) neural differentiation of progeny, and (4) integration into retinal circuitry (Goldman 2014). This is mediated by Increasing SHH, Notch decreasing allowing dedifferentiation influencing Stat3, which increases Ascl1a, that is linked to pluripotency factor Lin28, which when increased causes a decrease in let7. If we can replicate this in humans, we can drive MG led retinal regeneration.

To access the neurogenic potential of MG in mammals it's necessary to prevent the standard response to injury which results in the upregulation of reactive gliosis, and downregulation of proliferative genes. This may require decreasing the usually increased Notch upon injury to mimic the zebrafish response. Shh can stimulate mammalian injured and uninjured MG to proliferate (Wan et al., 2007) and p27KIP1 will also need to be controlled as it is an important factor to initiate the proliferative response. Ascl1/Mash1 is vital for neural differentiation and outgrowth, overexpression in injured young mice showed retinal regeneration (Ueki et al., 2015), along with histone deacetylase inhibition shows limited regeneration in adult mice (Jorstad et al., 2017). MicroRNAs are also being researched with miRNA-124 supressing miRNA let-7 inducing Ascl1 that results in 40 percent of MG to reprogrammed neuronal cell types (Wohl et al., 2019). Despite these advancements more research is needed before achieving therapeutic human retinal regeneration.

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