Title:

Understanding the gene regulatory network underlying zebrafish retina regeneration.

Abstract:

Visual impairment is one of the major problems faced by humanity. Despite the fact that the notion of retina regeneration seems implausible, unlike humans, there are vertebrates such as piscine and amphibians that have remarkable retina regeneration capabilities. Such organisms serve as a great tool to study retina regeneration, with zebrafish being a prominent example. Zebrafish, possess a significant regenerative response and with a retinal architecture similar to mammals, has emerged as the baseline model for studying retina regeneration. Upon retinal injury in zebrafish, Muller glia cells reprograms themselves to a multipotent stem cell-like state (Muller glial derived progenitor cells - MGPCs), which then proliferate further and give rise to various retinal cell types. Although many molecular signaling pathways and transcription factors are known to play an essential role during retina regeneration, one of the most crucial developmental signaling pathways, i.e., Sonic hedgehog (Shh) signaling pathway remained under-explored.

In this study, we show that the induction of Shh signaling is inevitable for zebrafish retina regeneration. Further, we report on a *let-7* microRNA-mediated stringent translational regulation of the components of Shh signaling such as *sonic hedgehog a* (*shha*), *sonic hedgehog b* (*shhb*), *patched1* (*ptch1*) and *smoothened* (*smo*). We also show the direct necessity of Shh signaling for the induction of pivotal transcription factor genes like *ascl1a, zic2b foxn4* and a RNA binding protein, *lin28a*. Interestingly, Matrix metalloproteinase-9 (Mmp9) causes the

initiation of Shh signaling for reprograming the Muller glial cells to MGPCs. Further investigation showed the repressive role of hairy enhancer of split-related (Her4.1, an effector of Notch signaling) in controlling the expression of *mmp9,* precisely in proliferating Muller glial cells. We believe that these novel findings pave the way to design new therapeutic strategies to treat retinal diseases in humans.