Title:	Understanding the molecular mechanisms of Mycs and Hdacs to control Her4.1/Lin28a/let-7 regulatory axis during zebrafish retina regeneration
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Abstract:	Vision loss due to retinal damage is till date a major health issue prevalent in society. In mammals, retina, being a part of the Central Nervous System (CNS), does not possess the ability to regenerate after an insult. Surprisingly, other vertebrates such as teleosts or urodeles possess remarkable regenerative potential in various tissues or organs. Zebrafish (Danio rerio), being one of the most extensively studied teleosts, serves as a great model organism to study regeneration of retina. Besides, being one of the most easily accessible parts of the CNS, retina serves as an ideal model system for studying the detailed molecular mechanisms underlying a successful retinal regeneration. Following an injury, Muller Glia (MG) cells, the only type of glial cells present in the retina, de-differentiate to form Muller glial derived progenitor cells (MGPCs) with stem cell-like properties which further proliferate and differentiate to all retinal cell types across every retinal layer, including MG itself, to compensate for the damage. Till now, a plethora of genetic factors including transcriptional activators (e.g. Ascl1a), transcriptional repressors (e.g. Insm1a, Her4.1), pluripotency-inducing factors (e.g. Lin28a), growth factors (e.g. Hb-egf), cytokines (e.g. interleukins), and, epigenetic modifiers (e.g. Dnmts) have been identified to play significant roles regulating the cellular process of retina regeneration. In spite of accumulation of this vast knowledge about the molecular regulators of retina regeneration in zebrafish, therapeutic interventions towards successful mammalian retinal regeneration still remains an unsolved enigma in mammals, demanding further investigation. In this study, we report rapid and MGPCs-associated induction of zebrafish Myc genes, namely myca and mycb which are necessary for a successful retinal repair. We also show the stringent regulation of mycb by previously characterized Ascl1a/Insm1a regulatory axis. Further, our study places Mycb, which is a de facto transcriptional activator, as a dual regulator acting on regeneration associated Lin28a/let-7 regulatory axis. We also show regeneration associated Delta/Notch signaling controls the extent of the injury responsive zone by negatively regulating mycb. Further to elucidate the mechanism underlying the negative regulation of Lin28a by Mycb, we show physical collaboration of Histone de-acetylase1 (Hdac1) with Mycb to repress lin28a and control proliferation. Besides Hdac1, we also found that several other Hdacs to be regulated post-retinal injury and inhibition of Hdacs resulted in impaired but reversible blockade of MGPCs proliferation fine-tuned by Her4.1/cytokines axis. Taken together, our study, not only places Myca/b and Hdacs as key regulators of the molecular mechanisms underlying zebrafish retina regeneration, but it also opens new possibilities for therapeutic interventions towards successful mammalian retina regeneration.
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