Title:	Understanding the role of multifaceted transcription factor Yin-Yang1 during zebrafish retina regeneration
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Abstract:	Globally, 7.7 million population suffer from glaucoma and 3.9 million from diabetic retinopathy worldwide as per World Health Organization 2021. Damage to the retina in such pathological conditions often leads to complete vision loss or blindness in mammals. In contrast to mammals, Teleosts such as zebrafish can regenerate their damaged retina and completely restore their lost vision. In response to injury, Müller glial cells of the retina undergo reprograming event and a series of signalling events starts, which bring about major epigenetic and molecular changes in the cells. These changes involve transcription factors, growth factors, cytokines, signalling pathways and epigenetic factors. Yin-Yang1(YY1) is a ubiquitous protein first discovered in 1991 and named differently by three independent groups. YY1 as a transcription factor plays a pivotal role during embryogenesis, development and normal homeostasis. It can regulate various genes by binding onto its promoter and can act as an activator or repressor, owing to its ability to choose the binding partner. Yy1 can interact with co-activators such as, HATs (histone acetyltransferase) and help open up the chromatin. Also, it can bind to co-repressors like Hdacs and Ezh2 and thus aids in forming heterochromatin. Yy1 also promotes enhancer-promoter interaction and forms TADs, a function similar to CTCF. Besides, differential binding partners, Yy1 carry out plethora of function because of myriads of post translational modification it undergoes. In our study, we explored the role of Yy1 during retina regeneration. We found that Yy1 acts as a pro-proliferative molecule, as knockdown of Yy1 leads to a decrease in the number of proliferating Müller glia while the overexpression of Yy1 increased proliferation. We also found that Yy1 positively regulates Lin28a expression, which in turn downregulates let-7a and causes an increases in the levels of Ascl1a, master regulator of retina regeneration. We further explored Notch signalling in Yy1 knockdown condition and found that Notch signalling indeed 3gets affected, which is also reflected in our RNA-seq data. Her4.1, an effector gene of Notch signalling, is downregulated by Yy1, which in turn upregulates Mmp9. Yy1 regulates BMP signalling, which is an important signalling during development. Previously, it was shown that BMP signalling is pro-proliferative in chick retina regeneration. We also found out that inhibition of BMP signalling leads to a decrease in proliferation in Yy1 dependent manner. Besides having an independent role as a pro-proliferative transcription factor, Yy1 acts synergistically with the BAF complex, a chromatin remodeler, to regulate many regeneration-associated genes. In this study, we also report that the function of Yy1 is dependent on its acetylation and subsequent timely deacetylation to evoke a successful regenerative response as acetylated- mimetic mutation of Yy1, surprisingly, caused a reduction in the number of proliferating MGPCs. Taken together, our study sheds light on the pro-proliferative role of Yy1 during retina regeneration and opens up new avenues to explore the therapeutic potential of Yy1.
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