Title:	Understanding the role of Matrix metalloprotease 14 (Mmp-14) and Furin during retina regeneration in zebrafish
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Abstract:	Unlike higher vertebrates, where retinal injury leads to scarring, zebrafish exhibits robust regenerative potential to restore the retinal structure and function. Injury to zebrafish retina induces Müller glia (MG) cells to dedifferentiate, proliferate and migrate to the various layers and differentiate into respective cell types to restore the retinal physiology by the help of various factors that assist tissue remodelling. Matrix Metalloproteases (MMPs) are known to be the primary Extracellular Matrix (ECM) remodellers which regulate the collagen and gelatin levels leading to ECM degradation. A class of MMPs, MT-MMP (membrane type MMPs), are known to be inserted in the membrane. We wanted to decipher the role of MMP-14 (MT1-MMP) in the process of zebrafish retina regeneration and understand the significance of its localisation on the membrane, unlike other classes of MMPs which are secreted into extracellular milieu. Upon checking the temporal expression pattern by RT-PCR, we found that mmp14a and its activator, furina, transcript levels are upregulated during dedifferentiation phase, when Muller glia starts to attain stemness. In- situ hybridisation and immunostaining revealed that mmp14a and furina are expressed in cells next to proliferating Müller Glia Progenitor Cells (MGPCs). Thus, we hypothesise that Mmp14 is expressed in neighbouring cells which activates pro-Mmp2 secreted into ECM. This activated form of mmp2 then act on MGPCs to aid proliferation. Upon inhibiting various established pro-proliferative signalling pathways such as TGF-beta, Mmp2/Mmp9 activation and prominent oncogenic long non-coding RNA, malat-1, the levels of mmp14a and furina transcripts were upregulated, suggesting that Mmp14a and Furina might be playing the crucial role in regeneration and hence system tries to upregulate them and maintain homeostasis. We also found Mmp14a and Furina to be anti- and pro- proliferative respectively. Furin is observed to be regulating various regeneration associated genes such as ascl1a, mmp9, zic2b and her4.1. Further, Furin is also observed to be helping in maintaining proliferation at 8dpi. Hence, to confirm the role of axis in the context of retina regeneration, we would like to overexpress mmp14a and then observe if the phenotype is rescued by Furin inhibition. And look at the regulation of various major pathways by the axis.
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