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Title:	Understanding the role of Pten and the molecular mechanisms underlying Pten/PI3K/Akt/mTOR pathway during zebrafish retina regeneration
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Abstract:	Visual organs have been accorded as the most crucial organs of the living beings and vision impairment becomes a major loss to the body. Mammals have lost the ability to regenerate their Central Nervous System (CNS), and retina, being a part of it, upon injury or any insult cannot regenerate in mammals. This renders them permanently disabled. But the robust regenerative potential of a teleost, zebrafish (Danio rerio), becomes a ray of hope as studying the mechanism underlying regeneration in zebrafish can enable us to develop therapeutic interventions in mammals. Zebrafish has been a great tool to study genetics and for a long time researchers have been engaged in probing into its regenerative mechanisms, as almost all its organs can regenerate. Retina regeneration is a cascade of reprogramming events involving specialized cells named Müller Glia (MG) which get activated, lose their fate and also adopt a retinal stem cell-like state upon any injury or stress. These multipotent stem cell-like MG derived progenitor cells (MGPCs) can proliferate and also form various retinal cell types, thus facilitating visual function restoration. But, as the MGPCs proliferate, they are under stringent control by multiple factors, which keep a check on the proliferative pace of these cells and prevent the regeneration process from going erratic. In this context, during retina regeneration, we have tried to explore the role of a tumor suppressor Pten which is a dual-specificity phosphatase. Till now Pten/PI3K/Akt/mTOR pathway has been well elucidated in various cancers, but it remains underexplored in retina regeneration. The pathway includes factors that promote proliferation like Akt and mTOR, and also factors that are anti-proliferative like Pten, all working in an orchestrated manner. Here we show that the downregulation of Pten from the MGPCs evokes a strong proliferative response by activating and increasing the levels of Akt. We observed that activated Akt leads to mTORC1 activation, which increases MGPCs proliferation. We propose the existence of a negative feedback control by mTORC1 on Akt. We delved deeper into the mechanism through which Pten contributes during retina regeneration and found the involvement of Mmp9/Notch signalling, β-catenin, and some other pathways also to regulate MGPCs proliferation. We also found that Pten itself is regulated by the Mycb-Hdac1 repressive complex and this regulation is further fine-tuned by the Tgf-β signalling pathway. Thus, we conclude by highlighting thecrucial role of Pten/PI3K/Akt/mTOR pathway in poising a successful regenerative response in the zebrafish retina.
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