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Title: Biphasic Role of Tgf - β Signaling during Müller Glia Reprogramming and Retinal Regeneration in

Zebrafish

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Keywords: Biological Sciences

Cell Biology

Functional Aspects of Cell Biology

Issue 2020

Date:

Publisher: Elsevier B.V.

Citation: iScience, 23(2)

Abstract:

Tgf- β signaling is a major antiproliferative pathway governing different biological functions, including cellular reprogramming. Upon injury, Müller glial cells of zebrafish retina reprogram to form progenitors (MGPCs) essential for regeneration. Here, the significance of Tgf- β signaling for inducing MGPCs is explored. Notably, Tgf- β signaling not only performs a pro-proliferative function but also is necessary for the expression of several regeneration-associated, essential transcription factor genes such as ascl1a, lin28a, oct4, sox2, and zebs and various microRNAs, namely, miR-200a, miR-200b, miR-143, and miR-145 during different phases of retinal regeneration. This study also found the indispensable role played by Mmp2/Mmp9 in the efficacy of Tgf- β signaling. Furthermore, the Tgf- β signaling is essential to cause cell cycle exit of MGPCs towards later phases of regeneration. Finally, the Delta-Notch signaling in collaboration with Tgf- β signaling regulates the critical factor, Her4.1. This study provides novel insights into the biphasic roles of Tgf-

 $\boldsymbol{\beta}$ signaling in zebrafish during retinal regeneration

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