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**Title:** let-7 MicroRNA-Mediated Regulation of Shh Signaling and the Gene Regulatory Network Is Essential for Retina Regeneration

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**Keywords:** Zebrafish  
Mmp9Zic2b  
Foxn4  
Lin28  
Retina  
Regeneration

**Issue Date:** 2018

**Publisher:** Elsevier B.V.

**Citation:** Cell Reports, 23(5), pp. 1409-1423

**Abstract:** Upon injury, Müller glia cells of the zebrafish retina reprogram themselves to progenitor cells with stem cell characteristics. This necessity for retina regeneration is often compromised in mammals. We explored the significance of developmentally inevitable Sonic hedgehog signaling and found its necessity in MG reprogramming during retina regeneration. We report on stringent translational regulation of sonic hedgehog, smoothened, and patched1 by let-7 microRNA, which is regulated by Lin28a, in Müller glia (MG)-derived progenitor cells (MGPCs). We also show Shh-signaling-mediated induction of Ascl1 in mouse and zebrafish retina. Moreover, Shh-signaling-dependent regulation of matrix metalloproteinase9, in turn, regulates Shha levels and genes essential for retina regeneration, such as lin28a, zic2b, and foxn4. These observations were further confirmed through whole-retina RNA-sequencing (RNA-seq) analysis. This mechanistic gene expression network could lead to a better understanding of retina regeneration and, consequently, aid in designing strategies for therapeutic intervention in human retinal diseases.

**URI:** <https://www.sciencedirect.com/science/article/pii/S221112471830531X>  
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