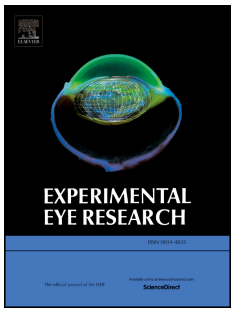
Accepted Manuscript



A role for Hippo/YAP-signaling in FGF-induced lens epithelial cell proliferation and fibre differentiation

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PII: S0014-4835(17)30672-3

DOI: 10.1016/j.exer.2018.01.014

Reference: YEXER 7269

To appear in: *Experimental Eye Research*

Received Date: 26 September 2017

Revised Date: 14 January 2018

Accepted Date: 16 January 2018

Please cite this article as: Dawes, L.J., Shelley, E.J., McAvoy, J.W., Lovicu, F.J., A role for Hippo/YAP-signaling in FGF-induced lens epithelial cell proliferation and fibre differentiation, *Experimental Eye Research* (2018), doi: 10.1016/j.exer.2018.01.014.

A role for Hippo/YAP-signaling in FGF-induced lens epithelial cell proliferation and fibre differentiation.

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Key words: Lens epithelial cells; cell proliferation; fibre differentiation; fibroblast growth factor; Yes Associated Protein; Hippo Pathway; MAPK/ERK-signaling.

Abstract

Recent studies indicate an important role for the transcriptional co-activator Yes-associated protein (YAP), and its regulatory pathway Hippo, in controlling cell growth and fate during lens development; however, the exogenous factors that promote this pathway are yet to be identified. Given that fibroblast growth factor (FGF)-signaling is an established regulator of lens cell behavior, the current study investigates the relationship between this pathway and Hippo/YAP-signaling during lens cell proliferation and fibre differentiation. Rat lens epithelial explants were cultured with FGF2 to induce epithelial cell proliferation or fibre differentiation. Immunolabeling methods were used to detect the expression of Hippo-signaling components, Total and Phosphorylated YAP, as well as fibre cell markers, Prox-1 and β-crystallin. FGF-induced lens cell proliferation was associated with a strong nuclear localisation of Total-YAP and low-level immuno-staining for phosphorylated-YAP. FGF-induced lens fibre differentiation was associated with a significant increase in cytoplasmic phosphorylated YAP (inactive state) and enhanced expression of core Hippo-signaling components. Inhibition of YAP with Verteporfin suppressed FGF-induced lens cell proliferation and ablated cell elongation during lens fibre differentiation. Inhibition of either FGFR- or MEK/ERK-signaling suppressed FGF-promoted YAP nuclear translocation. Here we propose that FGF promotes Hippo/YAP-signaling during lens cell proliferation and differentiation, with FGF-induced nuclear-YAP expression playing an essential role in promoting the proliferation of lens epithelial cells. An FGF-induced switch from proliferation to differentiation, hence regulation of lens growth, may play a key role in mediating Hippo suppression of YAP transcriptional activity.

1. Introduction

The growth of the lens throughout life involves proliferation of epithelial cells and their subsequent differentiation into secondary fibre cells (Lovicu and McAvoy, 2005). Lens epithelial cell proliferation occurs in the region just above the lens equator known as the germinative zone. The progeny of cell divisions migrate, or are displaced, below the equator into the transitional zone,