Research Highlight

A Mechanism for the Synergism of FGF- and Wnt-Signaling during Lens Fiber Cell Differentiation

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Although, to my knowledge, Lyu and Joo first suggested the promotion of lens fiber cell differentiation by Wnt signaling in FGF-treated lens epithelial explants in 2004,[1] the molecular nature of synergism between the two signaling pathways remained undefined. The current study by Dawes et al. exploits the lens epithelial explant system to gain mechanistic insight into the regulation of Wnt-signaling during lens fiber cell differentiation.[2] These investigators demonstrate that Fgf2, previously shown to induce robust fiber cell differentiation in these explants, increases the abundance of Wnt receptors (Fz3 and Fz6), as well as effectors of Wnt-signaling (Dvl2 and Dvl3). Fgf2 also induced the localization of Fz6 and pericentrin to the polarized leading edge of elongating fiber cells. They then demonstrate abrogation of Fgf-induced fiber cell elongation and β-crystallin expression by either of two inhibitors of Wnt signaling (Sfrp1 and IWP-2). Furthermore, these investigators showed that IWP-2 reduced the Fgf-induced upregulation of Dvl2, Dvl3, Fz, and the fiber cell protein, filensin, without having any effect on Fgf-induced down-regulation of the E-cadherin.

Wnt ligands can operate through a number of signal transduction pathways including canonical (involving β-catenin as a co-activator for TCF/Lef transcription factors), planar cell polarity, and the Wnt/calcium pathway. The McAvoy Laboratory, and others, previously confirmed the presence of components of the Wnt-frizzled/planar cell polarity (Wnt-Fz/PCP) pathway in lens fiber cells, and demonstrated that mutations in PCP pathway components or disruptions in Wnt-frizzled binding disrupt normal fiber cell orientation and suture formation.[3] Dawes et al. tested lens epithelial explants from TCF/Lef reporter mice to address the mechanism by which Wnt-signaling promotes fiber cell differentiation.[2] The TCF/Lef reporter remained silent in lens epithelial explants treated with either FGF or Wnt3a (a ligand known to activate canonical Wnt/β-catenin signaling), despite robust activation of the reporter gene in adherent ciliary body epithelium. This study represents a significant mechanistic advance in our understanding of the regulation of lens development by demonstrating how FGF can promote Wnt-Fz/PCP signaling to achieve the polarization and orientation necessary for fiber cell differentiation.

References

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