Ph.D. thesis: The role of Wnt signaling in embryonic development

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ABSTRACT

Wnt signaling plays important roles in multiple developmental processes. The binding of Wnt ligands to their receptors and coreceptors activates three main downstream pathways: canonical Wnt/β-catenin signaling, which results in the activation of β-catenin/Tcf mediated gene expression and noncanonical Wnt/PCP and Wnt/Ca^{2+} pathways. In this thesis, we aimed at studying the role of Wnt/β-catenin signaling during embryonic development, especially in the telencephalon and the eye.

Wnt/β-catenin signaling is essential for the maintenance of proliferation of neuronal progenitor cells and dorso-ventral specification during the telencephalon development. To provide further insights, we studied transcriptional targets of canonical Wnt signaling. We show that the ectopic activation of Wnt/β-catenin signaling results in the up-regulation of *Sp5* gene, which encodes a member of the Sp1 transcription factor family. A proximal promoter of *Sp5* gene contains five Tcf/Lef binding sites that mediate direct regulation of *Sp5* expression by canonical Wnt signaling. We further provide evidence that Sp5 works as a transcriptional repressor. Finally, our data strongly suggest that Sp5 has the same DNA binding specificity as Sp1 and represses Sp1 target genes such as *p21*. We conclude that Sp5 transcription factor mediates the downstream responses to Wnt/β-catenin signaling by directly repressing Sp1 target genes.

Wnt/β-catenin signaling is highly active in the dorsal retinal pigment epithelium (RPE) during eye development. To study the role of Wnt/β-catenin signaling in the RPE development, we conditionally inactivated or ectopically activated Wnt/β-catenin signaling in the RPE. Inactivation of Wnt/β-catenin signaling results in transdifferentiation of the RPE to the neural retina. In contrast, ectopic activation of Wnt/β-catenin signaling results in the disruption of the RPE patterning, indicating that precise spatial and temporal regulation of Wnt/β-catenin signaling is required for normal RPE development. We further provide evidence that *Otx2* and RPE-specific isoforms of *Mitf* are direct transcriptional targets of Wnt/β-catenin signaling. Combined, our data suggests that Wnt/β-catenin signaling plays an essential role in development of RPE by maintaining or inducing expression of *Mitf* and *Otx2*.

Wnt/β-catenin signaling is required to suppress lens formation in the periocular ectoderm during eye development and inhibition of the signaling in the presumptive lens placode is one of the prerequisites for lens development. But its exact mechanism is unknown. We show that Pax6 directly controls expression of several Wnt inhibitors such as *Sfrp1*, *Sfrp2*, and *Dkk1* in the presumptive lens. In accordance, absence of Pax6 function leads to aberrant canonical Wnt activity in the presumptive lens, which subsequently impairs lens development. Thus Pax6 is required for down-regulation of canonical Wnt/β-catenin signaling in the presumptive lens ectoderm.