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Tsukushi is a Novel Wnt Signaling Inhibitor Involved in Ciliary Body Formation in the Adult Mammalian Eye by Regulating Retinal Progenitor Cell Proliferation

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Abstract

Wnt signaling is involved in multiple developmental events during embryogenesis and it has also been implicated in adult tissue homeostasis. Several extracellular antagonists for Wnt signaling have been reported, but an inhibitor that specifically binds to the Fzd receptor and inhibits Wnt signaling has not been identified.

Retinal progenitor cells (RPCs) are located at the ciliary body (CB) of the mammalian eye possessing several universal characteristics of stem cells, and their proliferation and differentiation are controlled under the influence of Wnt signaling. The molecular signals and the microenvironment that maintain them quiescent in their cellular niche in vivo, however, remain largely unclear.

Here, we show that Tsukushi (TSK), which is a soluble molecule belonging to the Small Leucine-Rich Proteoglycan (SLRP) family, is expressed in the CB of the adult mouse eye. Targeted inactivation of the TSK gene causes expansion of the CB in vivo and increases the ability of RPCs isolated from the CB to proliferate in vitro. We demonstrate that TSK binds to the Wnt receptor Fzd4 directly and can effectively antagonize Wnt signaling in retinal cells both in vivo and in vitro. Our results suggest that TSK can function as a niche molecule for RPCs and that their proliferation in the adult retina may be stimulated by modulating TSK activity, resulting in new avenues for studies of retinal regeneration.

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