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TCTN2 Maintains the Transition Zone Stability and Controls the Entrance of the Ciliary Membrane Protein into Primary Cilia

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Abstract : The transition zone (TZ) serves as a diffusion barrier to regulate the ins and outs of the proteins recruited to the primary cilia. TCTN2 is one of the TZ proteins and its mutation causes Joubert syndrome, a serious multi-organ disease. Despite its important medical relevance, the functions of TCTN2 remain elusive. Here we created a TCTN2 gene deleted retinal pigment epithelial cells (RPE1) using CRISPR/Cas9-based genome editing technique and used this knockout line to reveal roles of TCTN2. TCTN2 knockout RPE1 cells displayed a significantly reduced ciliogenesis or a shortened primary cilium length in the cilium-remaining population. Intraflagellar transport protein IFT88 aberrantly accumulated at the tip of TCTN2 deficient cells. Guanine nucleotide exchange factor Arl13B was mostly absent from the ciliary compartment, with a small population localizing at the ciliary tip. The deficient TZ was corroborated with the mislocalization of two other TZ proteins TMEM67 and MKS1. In addition, TCTN2 deficiency induced TZ impairment led to the suppression of Sonic hedgehog signaling in response to Smoothened (Smo) agonist. Together, depletion of TCTN2 destabilizes other TZ proteins and considerably alters the localization of key transport and signaling-associated proteins, including IFT88, Arl13B, and Smo.

Keywords : CRISPR/Cas9, primary cilia, Sonic hedgehog signaling, transition zone
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