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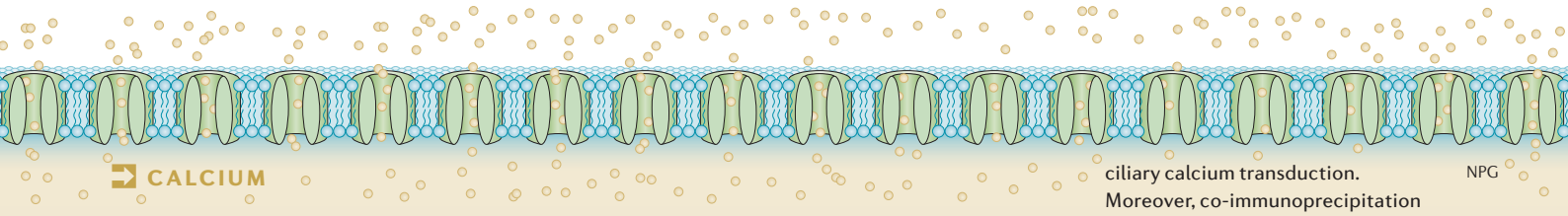

CALCIUM

An ion channel for cilia

The primary cilium is a sensory organelle that emanates from the cell surface of most eukaryotic cells. It is a key coordinator of signal transduction pathways such as Hedgehog (HH) signalling, and ciliary defects are associated with developmental abnormalities. Ion-conducting channels have been suggested to be involved in the transduction of sensory stimuli from the cilium, but the proteins responsible have not been identified.

Now, two papers by the Clapham group show that primary cilia are specialized compartments for calcium signalling, and that the transmembrane transient receptor potential (TRP) channel proteins PKD1L1 and PKD2L1 form a heterodimeric calcium channel that regulates ciliary calcium concentration and thereby ciliary signalling.

Both studies used a genetically encoded calcium sensor and whole-cell patch-clamp recordings to measure calcium signalling in fluorescently labelled individual primary cilia *in vivo*. Delling *et al.* ruptured the ciliary membrane at the tip of the cilium and showed that this leads to a wave of high ciliary calcium concentration that travelled to the ciliary base. Asking whether this increase in ciliary calcium affects calcium levels in the cytoplasm, they monitored changes in the calcium concentration at the ciliary–cytoplasm junction and found that the cytoplasmic calcium concentration remained unaffected. Furthermore, the resting calcium concentration in cilia was higher than that in the cytoplasm, which led the authors to propose that this compartmentalized calcium concentration is regulated by an ion channel.

Indeed, DeCaen *et al.* identified a calcium-selective ion channel that is highly expressed in primary cilia. Cells depleted of PKD1L1 and PKD2L1 by siRNA and *Pkd2l1*$^{-/-}$ mouse embryonic fibroblasts (MEFs) showed reduced ciliary calcium currents compared with wild type, suggesting that PKD1L1 and PKD2L1 initiate ciliary calcium transduction. Moreover, co-immunoprecipitation assays revealed that PKD1L1 and PKD2L1 interact. Thus, the data establish that PKD1L1 and PKD2L1 form a heterodimeric calcium channel.

> “ciliary calcium concentrations are controlled by the PKD1L1–PKD2L1 channel”

Finally, Delling *et al.* tested *Pkd2l1*$^{-/-}$ mice for potential ciliary defects and observed intestinal malrotation. This phenotype was previously associated with HH pathway defects during early development, so they tested whether the HH signalling is affected in *Pkd2l1*$^{-/-}$ MEFs. These cells exhibited decreased protein levels of the HH-activated glioma-associated transcription factor GLI1, and impaired accumulation of another HH pathway component, GLI2, at the ciliary tip compared with wild-type cells.

Together, these studies suggest that ciliary calcium concentrations are controlled by the PKD1L1–PKD2L1 channel and modulate HH signalling, and provide a mechanism by which cilia can rapidly respond to changes in the environment during development.

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ORIGINAL RESEARCH PAPERS Delling, M. *et al.* Primary cilia are specialized calcium signalling organelles. *Nature* **504**, 311–314 (2013) | DeCaen, P. C. *et al.* Direct recording and molecular identification of the calcium channel of primary cilia. *Nature* **504**, 315–318 (2013)