Mcidas mutant mice reveal a two-step process for the specification and differentiation of multiciliated cells in mammals

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Abstract

Motile cilia on multiciliated cells (MCCs) function in fluid clearance over epithelia. Studies with *Xenopus* embryos and patients with the congenital respiratory disorder reduced generation of multiple motile cilia (RGMC), have implicated the nuclear protein MCIDAS (MCI), in the transcriptional regulation of MCC specification and differentiation. Recently, a paralogous protein, Geminin Coiled-coil Domain Containing (GMNC), was also shown to be required for MCC formation. Surprisingly, in contrast to presently held view, we find that *Mci* mutant mice can specify MCC precursors. However, these precursors cannot produce multiple basal bodies, and mature into single ciliated cells. We identify an essential role for MCI in inducing deuterosome pathway components for production of multiple basal bodies. Moreover, GMNC and MCI associate differentially with cell-cycle regulators E2F4 and E2F5, which enables them to activate distinct sets of target genes (ciliary transcription factor genes versus basal body amplification genes). Our data establish a previously unrecognized two-step model for MCC development: GMNC functions in the initial step for MCC precursor specification. GMNC induces *Mci* expression that drives the second step of basal body production for multiciliation.

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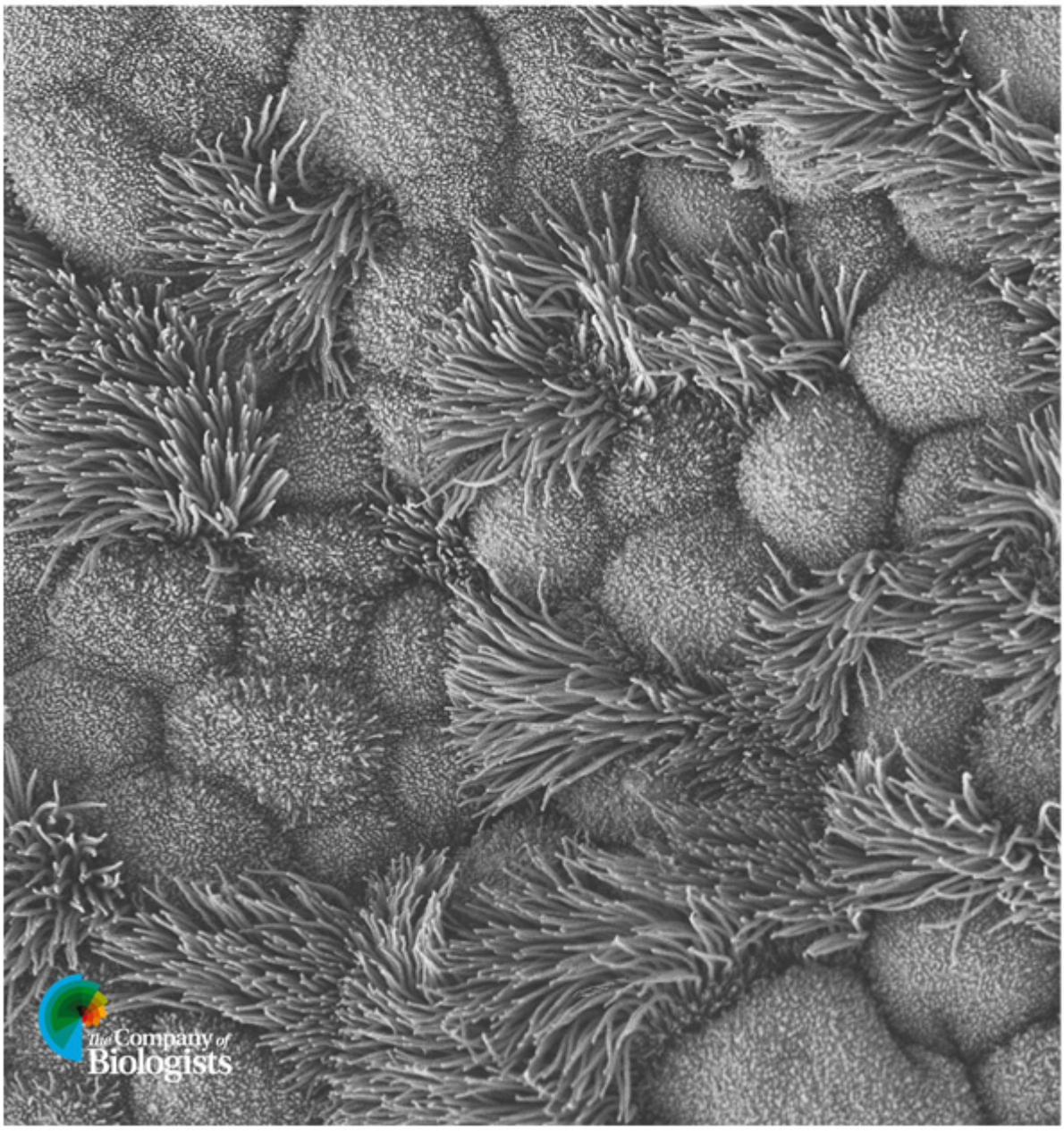

Cover: Scanning electron micrograph of multiciliated cells (MCCs) of the mouse trachea. Hundreds of cilia on each MCC beat metachronously to clear pathogen- and pollutant-laden mucus, and help maintain health of the airways. Image credit: Chee Peng Ng, Hao Lu and Sudipto Roy.