TUMORIGENESIS

No frills attached

“ cilia have an oncogenic or tumour-suppressive role depending on ... the oncogenic event

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Primary cilia are sites of regulation of the Hedgehog (HH) pathway, deregulation of which can cause basal cell carcinoma (BCC) or medulloblastoma. Two groups provide evidence that primary cilia have a functional role in modulating oncogenic HH signalling.

HH binding to its receptor, patched (*PTCH1*), activates smoothened (*SMO*), which relocates to the primary cilia to activate the transcription factor *GLI2*. In the absence of HH-*PTCH1* binding, proteolytic processing of *GLI3* (which is dependent on primary cilia) forms *GLI3-R*, which represses *GLI2*-mediated transactivation. To examine whether cilia are important

in tumours in which HH signalling is deregulated, Wong and colleagues used a conditional mouse model of BCC. In this model, tamoxifen treatment induces the expression of a constitutively active SMO mutant (*SmoM2*) and ablates either *Kif3a* or *Ift88*, which are required for ciliogenesis. Loss of cilia suppressed *SmoM2*-induced tumorigenesis, and the HH target genes *Gli1*, *Gli2* and *Ptch1* were not induced. To clarify whether cilia modulate the activity of *GLI2*, the authors used mice in which a constitutively active *GLI2* mutant (*GLI2ΔN*) is conditionally expressed and in which *Kif3a* or *Ift88* is conditionally ablated. Loss of cilia significantly accelerated *GLI2ΔN*-induced tumorigenesis and decreased the levels of *GLI3-R*, which corresponded to increased expression of some HH target genes. Moreover, inhibition of *GLI3* further increased the expression of *GLI2*, indicating that cilium-mediated formation of *GLI3-R* is required to suppress *GLI2*-mediated tumorigenesis, whereas cilia are essential for tumorigenesis when the upstream pathway is activated.

In another paper, Han and colleagues used a yellow fluorescent protein-tagged *SMOM2* mutant to induce medulloblastoma in mice. They found that *SMOM2* localized to primary cilia and that loss of cilia — through the ablation of *Kif3a* or *Ift88* — prevented the formation of medulloblastoma. Surprisingly, they found that in mice conditionally expressing *GLI2ΔN* medulloblastoma develops only

when cilia are ablated by removing *Kif3a* or *Ift88*. Gene expression profiling of *GLI2ΔN*- and *SMOM2*-induced tumours revealed that they were similar. However, *GLI3* was downregulated in *GLI2ΔN* tumours, and heterozygous loss of *Gli3* reduced the latency of *GLI2ΔN* tumorigenesis, indicating that loss of *GLI3* processing could account for the differing effects caused by loss of primary cilia.

So, what is the relevance to human disease? Wong and colleagues analysed eight human BCCs, and found that five were extensively ciliated. Han and colleagues analysed 38 human medulloblastoma samples and found that desmoplastic medulloblastomas were largely ciliated (5 of 6) and anaplastic medulloblastomas were associated with the absence of cilia (8 of 9). Furthermore, they analysed the gene expression profile data of 24 of the samples and found that ciliated cells were almost exclusively associated with tumours in which HH or Wnt signalling was activated.

Together, these data indicate that cilia have an oncogenic or tumour-suppressive role depending on whether the oncogenic event is activation of the upstream or downstream stages of the HH signalling pathway.

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ORIGINAL RESEARCH PAPERS Wong, Y. S. et al. Primary cilia can both mediate and suppress Hedgehog pathway-dependent tumorigenesis. *Nature Med.* 23 Aug 2009 (doi:10.1038/nm.2011) | Han, Y.-G. et al. Dual and opposing roles of primary cilia in medulloblastoma development. *Nature Med.* 23 Aug 2009 (doi:10.1038/nm.2020)