IN THE SPOTLIGHT

Losers of Primary Cilia Gain the Benefit of Survival

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Summary: In this issue, Zhao and colleagues demonstrate that loss of primary cilia in medulloblastoma cells confers resistance to the Smoothened (SMO) inhibitor sonidegib. When treated with sonidegib, medulloblastoma cells lost their cilia and gained resistance. Surprisingly, loss of cilia is associated with recurrent mutations in ciliogenesis genes that are eventually able to drive drug resistance. These findings uncover a previously unknown mechanism of cancer cells in gaining a “persister-like” state against anticancer agents at the expense of losing primary cilia. Cancer Discov; 7(12); 1374–5. ©2017 AACR.

See related article by Zhao et al., p. 1436 (7).

Primary cilia are microtubule-based organelles protruding from the surface of most vertebrate cells, functioning as a cellular antenna for sensing and responding to the extracellular environment (Fig. 1). Among cellular organelles, cilia have a unique feature, with assembly occurring during cell-cycle exit (G1–G0) and disassembly coinciding with cell-cycle reentry (G1/S to M). Typically, a cilium is anchored to the cell’s surface by the basal body, which develops from the mother centriole of the centrosome (1–3).

Cilia harbor core components of the Hedgehog (HH) pathway essential for HH signal transduction in response to developmental signals (4). Thus, HH signaling in embryonic stem cells, adult stem cells, and tumors depends on the cilium. Basal cell carcinoma (BCC) and medulloblastoma are examples of cancer types that are heavily dependent on HH signaling for their continuous cell proliferation. There are multiple modes of HH signaling activation in medulloblastoma. For example, when the HH pathway is activated, Smoothened (SMO), a G-protein–coupled receptor-like molecule, gets directed into cilia to inhibit Suppressor of fused (SUFU), a negative regulator of HH signaling. This results in activating GLI proteins, which can transcriptionally activate the HH signaling program causing a hyperactive HH pathway to drive proliferation and tumor growth (4–6). Through this signaling cascade, cilia are believed to enable HH signaling during normal development as well as oncogenic HH signaling (Fig. 1A). Thus, it is expected that antagonizing HH signaling will have a beneficial effect in controlling BCC and medulloblastoma proliferation. Indeed, vismodegib and sonidegib, the first SMO inhibitors used as anticancer drugs, have initially shown promising effects in BCC and medulloblastoma, but their effects were short-lived due to the emergence of drug resistance (Fig. 1B and C).

Although the search for resistance mechanisms has deepened in multiple angles, Zhao and colleagues identified a resistance mechanism occurring just at the surface of cells: the loss of cilia (7). Although loss of cilia during tumor formation is not completely unexpected, the mechanistic insights from their data demonstrate a surprising finding that cilia loss unexpectedly protects tumor cells from SMO inhibitors. Using a genomewide transposon mutagenesis screen in HH signaling–dependent medulloblastoma cells, Zhao and colleagues have elegantly identified SUFU and oral facial digital syndrome 1 (OFD1) as being culprit genes. Their analysis further reveals that recurrent mutations in OFD1 result in loss of cilia, which confers resistance to SMO inhibitors (1 µM). As a result, tumors that lack cilia ultimately gain the phenotype of a “persister state” and grow in a GLI2-dependent manner. Importantly, the described mechanism of therapeutic resistance is occurring in human patients. These aspects address an outstanding question of how a resistance mechanism could develop in HH signaling–dependent malignant tumors (Fig. 1C; ref. 7).

The proposed mechanism is rather paradoxical, as cilia are essential for SMO activation and GLI processing. What is the selective advantage of losing cilia, and what is the alternative source for HH signaling in these cells? Despite these questions remaining incompletely answered, the surprising experimental evidence suggests that upon losing cilia, the proteolytic processing of GLI2 is impaired, and as a result the truncated repressor form of GLI2 (GLI2-R) is not generated. This finding suggests that the cilium is a GLI processing hub and explains why upon ciliu loss, downstream HH signaling is constitutively active due to the presence of unprocessed full-length GLI2 (GLI2-FL; ref. 7). Thus, cilia play a prime role in trafficing the required levels of HH signaling, and cilia loss enables low but constitutive HH signaling downstream to SMO (Fig. 1C). The current work illuminates two important aspects that will have a major impact on the cell biology of cancer and cilia. First, the importance of having cilia in normal cells, and second, reintroducing cilia as an attractive hypothesis to counteract drug resistance in cancer cells that have lost cilia (Fig. 1D).

Some questions remain open and offer multiple interpretations. OFD1 is a centriolar satellite protein, whose removal leads to ciliogenesis (8, 9). OFD1 is also a component of the cilia disassembly complex, which is recruited at the ciliary base for timely ciliu disassembly (3). Thus, inefficient OFD1 recruitment or depletion of overall OFD1 levels in cells is expected to induce cilia assembly or delay cilia disassembly. Indeed, this has been shown in normal and cancer.
Figure 1. Cilium loss conferring resistance in HH signaling-dependent medulloblastoma and BCC cells. A, HH components for HH signal transduction in a cilium. B, Inactivation of HH signaling in medulloblastoma and BCC. C, Cilia loss due to OFD1 mutation (asterisk) and development of resistance against sonidegib. D, Cilium reintroduction by targeting cilia disassembly complex as a potential mechanism to resensitize cells to inhibitors and to reset HH signaling.

cells. Failure of OFD1 recruitment causes retarded cilia disassembly in human fibroblasts, and depletion of OFD1 can induce ciliogenesis in breast cancer cells (3, 9). The current finding demonstrating that the loss of OFD1 protein results in cilia loss may suggest altered functions of OFD1 depending on its level during ciliogenesis. It is also conceivable that background mutations in multiple ciliogenesis genes upon sonidegib treatment might also account for the observed differences in terms of cilia loss or cilia induction.

The authors propose alternative strategies to overcome SMO inhibitor resistance by using arsenic trioxide, a known GLI inhibitor, and JQ1, a BET bromodomain inhibitor that has been shown in preclinical studies to affect the epigenetic landscape and have antitumor activity in the SHH subgroup of medulloblastoma. Nevertheless, the current data demonstrating that cilia loss confers SMO inhibitor resistance opens up an obvious question as to whether reintroducing cilia can be a way to reset aberrant HH signaling and resensitize cells for inhibitors (Fig. 1D). Although this strategy may offer an advantage against drug resistance, identifying mechanisms to reintroduce cilia requires an in-depth understanding of cilia assembly and disassembly mechanisms in normal and cancer cells. Despite these limitations, cilia-regulating signaling pathways in drug-resistant cancers offer new avenues to target ciliary functions for the treatment of human cancers. Taken together, cilia loss as a mechanism to gain resistance even in tumor types that are dependent on cilia-mediated HH signaling highlights the potential importance of dissecting and targeting the mechanisms of cilia loss.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We are grateful to members of our laboratory for feedback. This work is supported by the Fritz Thyssen Foundation, Germany (20.16.0.027 MN).

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*Cancer Discov* 2017;7:1374-1375.

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