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Medulloblastoma: A problem of developmental biology

The identification of *SUFU* mutations in desmoplastic medulloblastoma provides new insights into vertebrate Hedgehog signaling and brain tumor formation.

Medulloblastoma, a primitive neuroectodermal tumor of the posterior fossa, is the most common central nervous system (CNS) malignancy of childhood. Despite aggressive multimodal therapy with surgery, radiation, and chemotherapy, 5-year survival rates have only recently approached >60% (Packer et al., 1999). In this preview we will address the genetic underpinnings of medulloblastoma and the role that Sonic hedgehog (Shh) signaling plays in this disease. Recent work by Taylor et al. (2002) extends our understanding of medulloblastoma oncogenesis and its relationship to normal developmental programs.

Medulloblastomas are thought to derive from immature granule cells of the cerebellum and comprise several histological and prognostic subgroups. The desmoplastic subtype is distinguished from "classic" medulloblastoma by the presence of relatively acellular nodules within the otherwise densely cellular sea of malignant cells. Expression of particular markers, such as TrkC, in tumor cells, has been shown to predict a relatively favorable outcome (Louis et al., 2002). A significant advance in our understanding of medulloblastoma tumorigenesis was the recognition that mutations of the Shh receptor, *Patched (PTCH),* were strongly associated with desmoplastic medulloblastoma. Germline *PTCH* mutations are etiologic in Gorlin's syndrome (also called Nevoid Basal Cell Carcinoma Syndrome), which is characterized by developmental anomalies and high rates of both basal cell carcinoma and medulloblastoma. Moreover, about 10%–20% of sporadic tumors, typically the desmoplastic variant, contain mutations within the Shh-PTCH pathway (Louis et al., 2002).

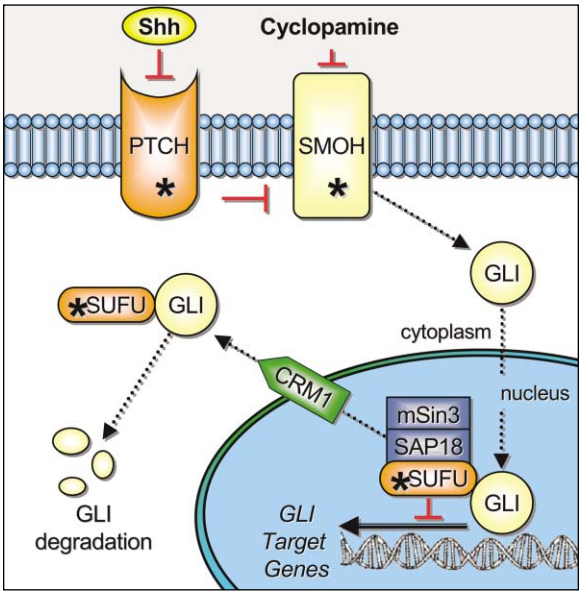

Figure 1. Mutations in Hedgehog (Hh) signaling predispose to tumorigenesis

Mutant alleles of *PTCH* and *SMOH* that result in activation of Hedgehog signaling are etiologic in basal cell carcinoma and medulloblastoma. Whether SMOH signaling directly regulates GLI activity is unclear. Recent work implicates *SUFU* as a functional repressor of GLI proteins that are thought to mediate activation of Hh transcriptional targets (Taylor et al., 2002). SUFU proteins in the nucleus repress GLI transcriptional activity by recruiting SAP18, a component of the mSin3 and histone deacetylase complex (Cheng and Bishop, 2002). Furthermore, SUFU exports GLI from the nucleus and the cytoplasm, where is targeted for degradation. Together, mutations in *PTCH, SMOH*, and *SUFU* (indicated by asterisks) account for the majority of cases of human desmoplastic medulloblastoma. Note that the cartoon represents a simplified scheme for vertebrate Hh signaling with particular emphasis on oncogenic mutations. For detailed summary of invertebrate Hh signaling, see Ingham and McMahon (2001).

Shh signaling is essential for the development of the mammalian CNS and is the major mitogenic pathway regulating proliferation of immature granule cells of the cerebellum (Wechsler-Reya and Scott, 2001). *hedgehog* was originally identified as a "segment polarity" gene by

Nusslien-Volhard and Wieschaus in a mutational screen of *Drosophila* embryos, and its vertebrate orthologs take their names from hedgehog species, both real and virtual (Ingham and McMahon, 2001). Hedgehog proteins bind to the multipass receptor PTCH, which functions as a repressor of the pathway. Shh binding to PTCH is thought to relieve inhibition of Smoothened (SMOH), a seven-span transmembrane protein with homology to G protein-coupled receptors (Figure 1). This results in upregulation of Shh transcriptional targets, including *PTCH* itself as well as members of the vertebrate *GLI* family of zinc-finger transcription factors. GLI proteins are then thought to mediate the transcriptional program of Hedgehog signaling (Ingham and McMahon, 2001; Ruiz-i-Altabla et al., 2002).

SUFU, encoding the human ortholog of *Drosophila suppressor of fused,* appears to have a conserved role in the repression of Hedgehog signaling. However, genetic and biochemical studies suggest that its mode of action is distinct from that of PTCH. SUFU exerts its repressor role by physically interacting with GLI proteins in both the cytoplasm and the nucleus (Ingham and McMahon, 2001). In the cytoplasm, SUFU can sequester GLI proteins, rendering them susceptible to degradation, while in the nucleus SUFU appears to recruit SAP18, a component of the mSin3 and histone deacetylase complex, to form a repressor unit that inhibits GLI transcriptional activity (Cheng and Bishop, 2002). Finally, SUFU promotes the active export of GLI proteins from the nucleus via a CRM-1-dependent mechanism (Figure 1).

Although mutations in *PTCH* have been found in medulloblastoma and its oncogenic properties have been validated in animal models, these lesions only account for a minority of cases (~10%; Wechsler-Reya and Scott, 2001). The phenotype of the index case studied by Taylor and coworkers (2002) was suggestive of Gorlin's syndrome; however, the patient was found to have intact *PTCH* loci. This prompted them to investigate mutations in other Shh pathway elements. Several chromosomal abnormalities are commonly associated with medulloblastoma including loss of chromosome 10q in 41% of cases. Interestingly, *SUFU* localized to chromosome 10q24.3 and, indeed, Taylor et al. (2002) confirmed mutation of *SUFU* in the index case. They went on to identify three further independent *SUFU* mutations in a series of 46 medulloblastomas. The *SUFU* mutations were associated with the desmoplastic subtype of medulloblastoma, and loss of heterozygosity was found in each case. Because most of these mutations predicted truncated SUFU proteins, the authors tested mutant forms for activity in vitro. This revealed that mutant SUFU proteins were unable to bind to GLI1 or GLI2 or to promote the export of GLI from the nucleus. Additionally, mutant SUFU was unable to suppress GLI-dependent transcription. Together, these data link the loss of *SUFU* function to the formation of desmoplastic medulloblastoma and provide the first demonstration of functional requirements for *SUFU* in vertebrate organisms. The work is significant in a further respect. Although mutations of *PTCH* and *SMOH* are thought to result in activation of Hh targets, it has not been clear whether GLI or other Hh targets are responsible for the oncogenic effects. The findings of Taylor et al. (2002) implicate GLI activity per se in the genesis of human medulloblastomas.

It thus appears that mutations in the Shh pathway will account for most cases of desmoplastic medulloblastoma (Pomeroy et al., 2002). Recent clinical success with tyrosine kinase and farnesyltransferase inhibitors has focused attention on generation of chemotherapeutic agents based on a thorough understanding of tumor biology. Indeed, jervine and cyclopamine, two plant-derived alkaloids first described for their etiologic role in endemic holoprosencephaly in livestock, are potent and relatively specific inhibitors of Hedgehog signaling and could prove a useful class of agents to employ in certain cases of desmoplastic medulloblastoma (Figure 1).

In the monograph *Cancer: A Problem of Developmental Biology*, G. Barry Pierce and colleagues predicted that a precise understanding of the developmental milieu would yield important insights into mechanisms that control cancer (Pierce et al., 1978). Functional studies of *PTCH* tumor suppressor function coupled with the findings of Taylor et al. (2002) comprise clear examples of how similar mechanisms can underlie both CNS development and formation of medulloblastoma. Such interdisciplinary crossfertilization is likely to yield further insight into brain tumorigenesis and aid in the generation of tumor-specific therapeutic strategies.

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Acknowledgments

The authors thank Mark Kieran, Charles Stiles, Kieth Ligon, and Rosalind Segal for comments and the NIH for support. D.H.R. is a Kimmel Scholar. Due to space limitations, it was only possible to list primary references that do not appear in the cited reviews.

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