Hedgehog-GLI Pathway in Medulloblastoma

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Medulloblastoma (MB), the most common malignant brain tumor in children, arises in the cerebellum. Aberrant activation of the sonic hedgehog (SHH) pathway has been unambiguously tied to the etiology of one subtype of the disease. Although the majority of tumors arise through somatic mutations, familial predisposition to MB is well known to occur in association with germline mutations of the SHH receptor patched (PTCH), a repressor in the SHH pathway, in a cohort of Li-Fraumeni patients with MB. They discovered germline SUFU mutations in eight of these patients, most commonly in introns.

Developmentally important signaling pathways are frequently recapitulated in cancer, and SHH-driven MB is one such classic example. As germline mutations in SUFU deregulate SHH signaling and potentially other signaling pathways, understanding how the SUFU mutations lead to oncogenic transformation is of crucial importance.

The cerebellum begins to form early on in embryonic development but does not fully mature until a few months after birth. This prolonged maturation makes the cerebellum especially vulnerable to developmental abnormalities and cancer. SHH is secreted by the Purkinje neurons that are present underneath the external granular layer of the developing cerebellum. SHH drives proliferation of granule neuron precursors to orchestrate cerebellar patterning and dictate the size of the organ. It is not surprising that deregulated hyperactive SHH signaling in granule neuron precursors during cerebellar development is a primary event during MB pathogenesis.22

The ability of SHH to control cerebellar pattern emerges from its anterior/posterior patterning, induction of polarity, and

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**Fig 1**: Mutations in SUFU or PTCH lead to activation of the hedgehog pathway. (A) In the absence of sonic hedgehog (SHH) ligand, patched (PTCH) receptor inhibits Smoothened (SMO) from accumulating in the cytoplasm. SMO exists in a nonactivating form (SMO0) in the cell, which is in equilibrium with an inactive cytosolic bound form (SMO1) and an active form (SMO2). Suppressor of fused (SUFU) inhibits G1 and G0 from entering the nucleus. The G1s are phosphorylated by CDK1 (calcium dependent kinase 1), leading to their inactivation and forming G1. SHH then functions as a transcriptional repressor on the S1 target genes. SUFU in combination with kinesin IFB1 antagonizes the somites to the microtubules. Binding of SHH to PTCH releases the repression on SMO, which allows for accumulation of active SMO in the nucleus. SMO accumulation in the cytoplasm reactivates the Suppressor of fused (SUFU) on the G1 transcription factors. Activated G1 then transcribes the nuclear and secondary expression of its target genes. (C) In cancer, when either PTCH or SUFU are inactivated because of mutations or otherwise degraded, the pathway is activated in the absence of SHH ligand. Even if SHH is not mutated in tumors, it may be preferentially disregulated by ubiquitination or by microRNA.