

SHH and GLI Protein Function in CNS Development and Disease

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The secreted glycoprotein Sonic hedgehog (Shh) triggers a signaling cascade that is involved in different aspects of the development of the early CNS, controlling cell differentiation, survival and proliferation (reviewed in 1-3). Moreover, deregulation of this pathway has been implicated in familiar (4,5), as well as sporadic cancers, which include basal cell carcinomas (BCCs) (6-12), rhabdomyosarcomas (RBs) (13), medulloblastomas (MBs) (14-18) and other types of brain tumors (19) (reviewed in 1,20). The study of Gli protein function, as the last known mediator of HH signals has provided insights into how ventral differentiation takes place in the early CNS (reviewed in 21) but also on how the alter dorsal brain grows (19). In this sense, it appears that there is a redeployment of a pathway used early in CNS development ventrally to take a major role in the growth and possibly the shaping of the major dorsal structures of the brain. The neocortex, the colliculi and the cerebellum as evolutionarily plastic structures that share the action of SHH from differentiated cells on precursor populations found at a distance. The SHH-GLI pathway, and in particular the function of each of the three GLI proteins thus appears to be critical in many aspects of pattern formation, including overall growth by affecting precursor cell number. On one hand, our studies of the Gli proteins have also taken us to investigate the role of these proteins in forebrain development, where their misfunction may underlie cases of holoprosencephaly. On the other hand, our studies and those of our colleagues indicate that inappropriate function of these GLI transcription factors leads to the initiation of a variety of tumors, including basal cell carcinomas, medulloblastomas and possibly gliomas. We propose that one of the major roles the SHH-GLI pathway plays in animal development is the modulation of precursor cell number, which in the correct scenarios leads to correct growth and pattern. Opposite defects in this pathway would therefore provoke diseases of mispatterning and undergrowth, such as holoprosencephaly, and diseases of mispatterning and overgrowth, such as brain cancer.

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Ruiz i Altaba A. (1999) Gli proteins and Hedgehog signaling: development and cancer. *Trends Genet* **15**, 418-25.

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Original Articles:

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