the mRNA cap binding translation initiation factor eIF-4E (Gingras et al., 2001). Strikingly, ectopic expression of eIF-4E is sufficient to phenocopy the ability of activated Ras to transform primary rodent cells in cooperation with Myc or E1A (Lazaris-Karatzas and Sonenberg, 1992). eIF-4E is inhibited by binding to 4E-BP and a set of related proteins, and this inhibition is relieved by Akt signaling through mTOR at the level of 4E-BP phosphorylation (Gingras et al., 1999). eIF-4E and 4E-BP have opposing effects on apoptosis, including roles in mediating the antiapoptotic effects of activated Ras (Polunovsky et al., 1996, 2000). Interestingly, recent work suggests that malignant transformation may be associated with a higher requirement for cap-dependent translation to inhibit apoptosis (Li et al., 2002). The Akt/mTOR pathway also activates the key translational regulatory kinase p70S6K (Jefferies et al., 1997), and the ability of Akt to transform cells is tightly linked to upregulation of p70S6K and downregulation of 4E-BP (Aoki et al., 2001). Taken together, these and other studies reveal a causal association between cell transformation and translational control by Ras/Akt signaling.

Holland and colleagues advance the association between Ras/Akt signaling and translation in cancer cells in two ways: first, by showing that Ras/Akt signaling rapidly influences the patterns of mRNA loading on polysomes and second, by defining the identity of a large set of genes that are regulated in this manner. As many receptor signaling pathways impinge on Ras and Akt, and thereby on translation initiation factors, it will be interesting to learn how much overlap there may be in the genes subjected to regulation at the level of polysomal mRNA recruitment. Furthermore, given the rapidity with which cells can respond to signaling through this level of regulation, it will be interesting to learn whether other signal transduction pathways use the same mechanism to drive transcription-independent programs of gene expression.

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# Developmental biology informs cancer: The emerging role of the hedgehog signaling pathway in upper gastrointestinal cancers

**The hedgehog (Hh) signaling pathway plays many roles in invertebrate and vertebrate development. For example, specific inhibition of sonic Hh expression is critical during early stages of pancreas organogenesis, but an active Hh pathway appears to be required for maintenance of adult endocrine functions. Mutational inactivation of the Hh pathway has been demonstrated in human malignancies of the skin, cerebellum, and skeletal muscle. Now, two papers implicate aberrant Hh signaling in human upper gastrointestinal cancers including those developing from the esophagus, stomach, biliary tract, and pancreas.**

Malignancies involving the upper gastrointestinal tract (esophagus, gastric, biliary, liver, and pancreas) represent some of the most biologically aggressive and therapeutically challenging cancers. In the United States, the number of patients diagnosed with these cancers in 2003 has been estimated at 70,000 with approximately 54,000 deaths. Pancreatic cancer alone will account for 30,000 deaths this year and remains one of the most treatment-refractory cancers despite aggressive use of conventional modalities such as surgery, radiation therapy, or chemotherapy.

Originally described in *Drosophila*, the hedgehog (Hh) signaling pathway is one of the most fundamental in embryonic development. Three mammalian Hh genes have been identified (sonic Hh [*SHh*], Indian Hh [*IHh*], and desert Hh [*DHh*]). Generally, this signal transduction pathway is responsible for patterning numerous structures including the axial skeleton, neural tube, limbs, lungs, skin, hair, and teeth. In addition, SHh has been demonstrated to be essential to

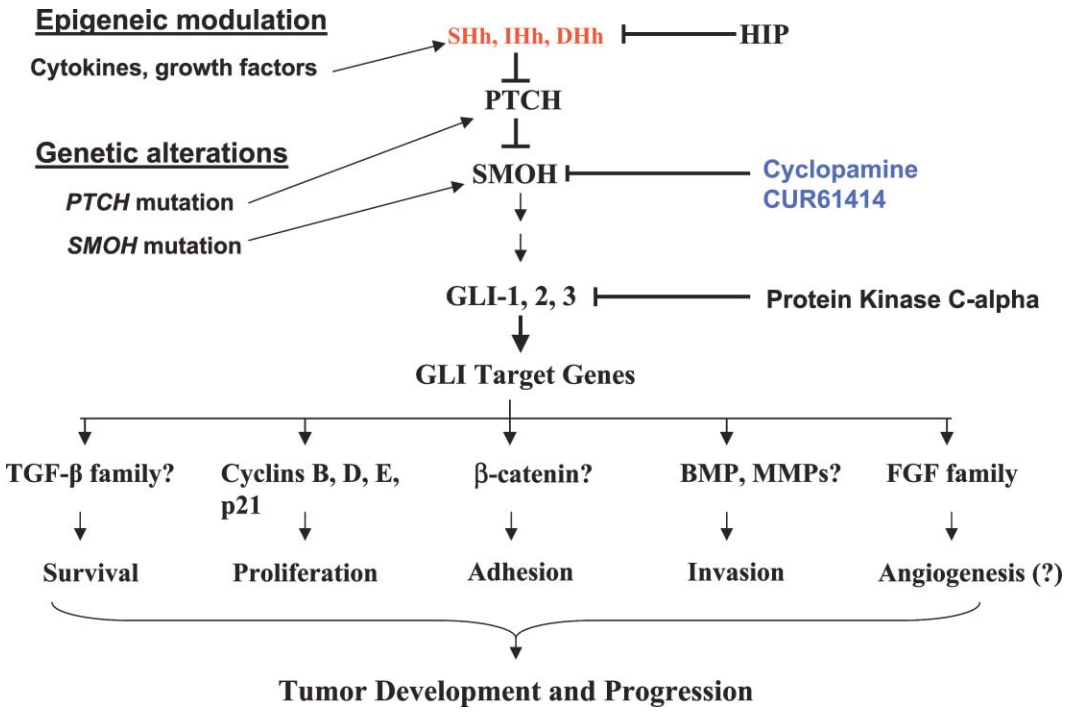


**Figure 1.** Hedgehog signaling, carcinogenesis, and potential therapeutic targets

Upregulation of Hh ligands may be mediated by epigenetic events. Mutations in PTCH and SHOH result in activation of hedgehog signaling and are causative in basal cell carcinoma and medulloblastoma. Gli proteins are thought to mediate activation of Hh transcriptional targets potentially important in tumorigenesis, progression, and metastasis. Abbreviations: SHh, sonic hedgehog; IHh, Indian hedgehog; DHh, desert hedgehog; HIP, hedgehog interacting protein; PTCH, patched; SMOH, smoothened; GLI; cubitus interruptus-like transcription factor involved in glioma formation.

normal foregut development, and SHh null mice show esophageal atresia/stenosis, tracheoesophageal fistula, and lung abnormalities. An Hh signaling model has been formulated based on studies in vertebrate systems (Figure 1). Hh proteins bind to a 12-pass transmembrane protein patched (PTCH), which is the ligand binding component of the receptor complex and functions as a repressor of the pathway. SHh binding to PTCH relieves inhibition of smoothened (SMOH), which is a 7-pass transmembrane protein with homology to G protein-coupled receptors and is responsible for transducing the Hh signal. In the absence of Hh binding, PTCH maintains SMOH in an inactive state, thus inhibiting signaling to downstream proteins. With the binding of Hh, PTCH inhibition of SMOH is released and the signal is transduced. 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 mediate the transcriptional program of Hedgehog signaling (Ingham and McMahon, 2001; Ruiz i Altaba et al., 2002). Recent studies have suggested that multiple signaling pathways, including TGF-β, FGF, notch, and Hh pathways regulate and interact with each other to govern GI tract and pancreas development. Although the exact roles of each Hh ligand in pancreas development continue to be elucidated, it has been demonstrated that SHh-induced signals block pancreas development, whereas the other Hh ligands appear to control β cell development and may function at later stages in mature pancreatic tissue (Hebrok, 2003).

The importance of the Hh signaling pathway in tumorigenesis was initially suggested by the identification of the *Gli1* gene for its involvement in glioma formation, the *Wn1* gene in murine mammary tumorigenesis, and the *Smad* genes in the formation of a range of tumor types and was firmly established through the discovery of inactivating mutations in the *PTCH* gene in patients with familial and sporadic basal cell carcinoma. Other tumors that carry *PTCH* mutations include esophageal squamous cell sarcomas and transitional cell carcinomas of the bladder (Aboulkassim et al., 2003). Cancer-associated alterations have also been demonstrated for other components of the Hh signaling pathway, including activating mutations in the *SMOH* gene, and, based on the role of SHh in lung development, Hh signaling pathway has been demonstrated to be active in a subset of small cell lung cancers (Watkins et al., 2003).

Two recent studies published in *Nature* extend the concept that Hh signaling is activated in human cancer. These two studies provide evidence that overexpression of *SHh* with subsequent activation of SMOH can result in a cancer-inducing phenotype in some gastrointestinal cancers that mimics inactivation of *PTCH* in basal cell carcinomas. Berman and colleagues (Berman et al., 2003) demonstrated that

upper gastrointestinal malignancies derived from the esophagus, biliary tract, stomach, and pancreas display increased Hh pathway activity. Further, they showed that cell growth was mediated by endogenous expression of Hh ligands through demonstration of the growth inhibitory activity of Hh-neutralizing antibody and the growth stimulatory activity of exogenously added Hh ligand. Finally, cyclopamine, a steroidal alkaloid that inhibits Hh signaling through direct interaction with SMOH, was shown to suppress cell growth in vitro and produce durable regression of a cholangiocarcinoma cell line in vivo.

The observations of Berman et al. on pancreatic cancer cell lines have been amplified through the work of Thayer and colleagues (Thayer et al., 2003). These investigators demonstrated that SHh is abnormally overexpressed in pancreatic adenocarcinoma cells and pancreatic intraepithelial neoplastic lesions (PanINs) compared to normal pancreatic ductal epithelium. Interestingly, pancreata from transgenic mice overexpressing SHh displayed abnormal tubular structures that resemble early PanINs, and some of these PanIN-like lesions also harbored K-*ras* mutations and overexpressed Her2/*neu*. These later two molecular abnormalities are characteristic alterations found in early pancreatic ductal carcinogenesis. Like Berman et al., this group also found that the Hh signaling pathway is active in most pancreatic cancer cell lines and inhibition of Hh signaling by cyclopamine induced apoptosis and inhibited proliferation in a subset of these pancreatic cell lines. The reasons that some cell lines with apparent activation of Hh signaling remained resistant to cyclopamine are still unclear but will be important to understand as efforts proceed to target the Hh pathway for drug development.

The significance of these two papers cannot be underestimated. While further delineation of the role of Hh signaling in upper gastrointestinal cancers needs to proceed, it is apparent that this signal transduction pathway has relevance to a large group of human cancers providing new opportunities for the identification and subsequent validation of therapeutic targets. In addition, the suggestion that aberrant Hh signaling is an early event in pancreatic carcinogenesis opens opportunities to develop techniques to detect aberrant Hh signaling in pancreatic juice or pancreatic duct cytology specimens for the early diagnosis of premalignant PanINs.

Successfully targeting Hh signaling will require further insights into the role of this pathway in cancer. First, we will need to understand how altered Hh signaling contributes to carcinogenesis. Currently, we have very little perception of the underlying mechanisms that link these two processes. Second, there may be only subsets of GI cancer patients with dysregulated Hh pathways. Third, there may be redundancy and crosstalk within the Hh signaling pathway that may prevent biologically effective blockade (Grachtchouk et al., 2003; Weiner et al., 2002). And finally, Hh signaling may be critical to other normal physiologic processes such as tissue repair (Watkins et al., 2003). Nevertheless, the apparent requirement for Hh pathway activation in an important group of human cancers represents a potential therapeutic opportunity (Berman et al., 2002; Williams et al., 2003) that warrants further investigation.

In a broader sense, the observation that Hh signaling pathways are activated in some cancers supports the growing appreciation that the signaling pathways that control vertebrate embryonic development may also be important during human carcinogenesis. The observations that the Hh signaling pathway is activated in esophageal, gastric, biliary tract, and pancreatic cancers provides important new opportunities for the development of novel interventions that may be applicable to a large group of cancer patients who currently have only limited therapeutic options.

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