Review

The Prognostic Significance of the Hedgehog Signaling Pathway in Colorectal Cancer

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Abstract

Despite significant advances in the management of colorectal cancer (CRC) the identification of new prognostic biomarkers continues to be a challenge. Since its initial discovery, the role of the Hedgehog (Hh) signaling pathway in carcinogenesis has been extensively studied. We herein review and comment on the prognostic significance of the Hh signaling pathway in CRC. The differential expression of Hh pathway components between malignant and nonmalignant conditions as well as correlation of Hh activation markers with various clinicopathological parameters and the effect on disease-free survival, overall survival, and disease recurrence in patients with CRC is summarized and discussed. According to the studies reviewed herein the activation of the Hh pathway seems to be correlated with adverse clinicopathological features and worse survival. However, to date study results show significant variability with regard to the effect on outcomes. Such results need to be interpreted carefully and emphasize the need for further well designed studies to characterize the actual influence of the Hh pathway in CRC prognosis.

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Introduction

Colorectal cancer (CRC) is a common cancer responsible for significant morbidity and mortality (447,000 new CRC diagnoses in Europe in 2012 accounting for 215,000 deaths[1]). The estimated new diagnoses for 2015 in the United States are 133,000 and the estimated deaths almost 50,000.[2] Despite the significant advances in the management of this tumor type, identification of new prognostic biomarkers continues to be a challenge.

Since the initial discovery of the Hedgehog (Hh) signaling pathway in *Drosophila*[3] the role of the pathway in embryonic development and carcinogenesis has been extensively studied.[4,5] Mammals have 3 orthologues of the single *Drosophila Hh* gene: Sonic Hh (*Shh*), Indian Hh (*Ihh*), and Desert Hh (*Dhh*) that are expressed in a tissue-specific manner. When any of the ligands binds to the 12-pass transmembrane receptor Patched (Ptch) 1, the inhibitory effect exerted on the adjacent 7-pass membrane protein Smoothened (Smo) is relieved. This leads to full activation of Glioma-associated oncogene homologue (*Gli*) isoforms, to inhibition of their proteolytic processing, and to dissociation from the inhibitory protein Suppressor of Fused (Sufu), leading to translocation of Gli into the nucleus followed by induction of the expression of the target genes of the pathway. There are 3 *Gli* genes; *Gli1*, *Gli2*, and *Gli3*; *Gli2* and *Gli3* are constitutively expressed and *Gli1* is induced by Hh and constitutes a useful marker of pathway activation. In addition to *Gli1*, other common *Gli* target genes include *Ptch1* and Hh interacting protein (*Hip*). Ptch1 and Hip are negative regulators of the pathway by inhibition of Smo and by sequestering the ligands, respectively, and Gli1 is an activator of the pathway. Some studies suggest a paracrine mechanism through effects on the stromal cells that surround the tumor[6] and others preconceive an autocrine mechanism of action with direct effect of the ligands to the cancer cells (Figure 1).[7]

The significance of alterations in the Hh pathway have been investigated in several cancer types. *Gli1* has been shown to be amplified within glioma,[8] osteosarcoma, and rhabdomyosarcoma.[9]

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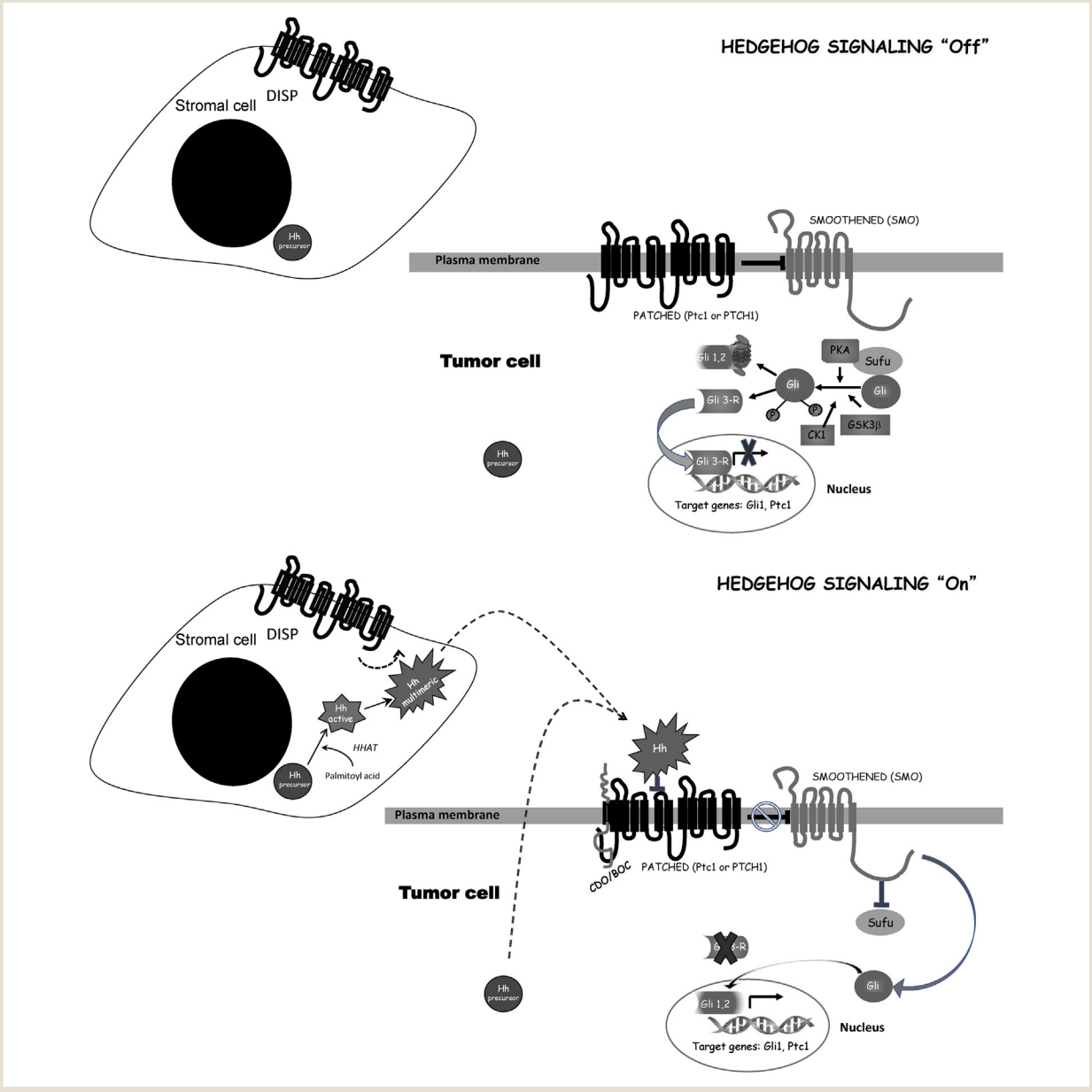
Figure 1 The Hedgehog (Hh) Proteins Comprise a Group of Secreted Proteins That Regulate Cell Growth, Differentiation, and Survival: Sonic Hh (Shh), Indian Hh (Ihh), and Desert Hh (Dhh). Sonic Hh is the Best Studied Ligand of the Hh Pathway in Vertebrates. In the Absence of the Ligand ("Off" State), the Patched (PTCH) Receptor Inhibits Smoothened (SMO), a 7-Transmembrane Receptor-Like (GPCR-Like) Protein Downstream in the Pathway. Glioma-Associated Oncogene Homologue (Gli) Proteins Are Then Sequestered by Suppression of Fused (Sufu), Which Is a Major Negative Regulator of the Hh Pathway and From Kinesin-Family Protein, Kif7 (Not Shown Here), Allowing for Gli Phosphorylation by PKA, GSK3β, and CK1, and Subsequent Processing Into Transcriptional Repressors (Through Cleavage of the Carboxy-Terminus, Not Shown Here) or Targeting for Degradation (Mediated by the E3 Ubiquitin Ligase β-TrCP). After Activation and Formation of the Multimeric Hh Ligand the Ligand Is Released From Dispatched (DISP) and Secreted From the Signaling Cell. Subsequent Binding of Hh ("On" State) to PTCH (and to the Coreceptors GAS1, CDON, and BOC, Not Shown) Alleviates This Inhibition and Activates SMO. SMO Then Mediates Downstream Signal Transduction That Includes Dissociation of Gli Proteins (the Transcriptional Effectors of the Hh Pathway). Gli Subsequently Translocates to the Nucleus and Initiates the Expression of the Target Genes (Transcription Factors *Gli 1, Gli 2, C-myc*, and *Cylcins D, E, Etc*) and Degradation of Gli 3 (Repressor of the Pathway). Hedgehog Acyltransferase (HHAT) Is Necessary for Post-Translational Palmitoylation of Hh. Absence of HHAT Results in Decreased Secretion of Hh. Signaling Might Be Either Autocrine (Shown) or Paracrine With the Ligand to Be Secreted Either From the Tumor Cell Toward the Stromal Cell (Not Shown) or in a Reverse Manner (ie, From the Stromal Cell Toward the Tumor Cell (Shown))



Abbreviations: BOC=Brother of CDO; CDON=Cell adhesion molecule-related/down-regulated by oncogenes; CK1=Casein Kinase 1; c-myc=c-myelocytomatosis; GAS1=growth arrest-specific 1; GSK3β=Glycogen Synthase Kinase 3β; PKA=Protein Kinase A; β-TrCP=beta-transducin repeat containing protein.