

Targeting the hedgehog pathway for gallbladder cancer therapy?

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Abstract: Gallbladder carcinoma is a fatal malignancy of hepatobiliary tract that is generally diagnosed at advanced stages of cancer because of its asymptomatic nature. Advanced GBC tumors are unresectable with poor prognosis. Improvement in GBC patient care requires better understanding of the biological signaling pathways and application of newly discovered drugs for cancer therapy. Herein, we discuss the possibilities and challenges in targeting the hedgehog pathway in gallbladder cancer therapy based on recent developments in the area.

Keywords: Gallbladder neoplasms; molecular targeted therapy; biliary tract cancer; hedgehog pathway

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Gallbladder carcinoma (GBC) is a highly aggressive malignancy of the hepatobiliary tract, the fifth most common gastrointestinal tumor. However, most patients with GBC are presented at the advanced stage carcinoma because of its asymptomatic nature (1). The aggressive tumor spreads in anatomically neighbouring areas, making it unresectable and “incurable”. In advanced GBC cases, the standard care involves combination chemotherapy with gemcitabine and cisplatin, it does not have a significant impact on the median overall survival which is less than 6 months after diagnosis. Long-term survival in small proportion of cases is primarily seen in those detected incidentally during routine cholecystectomy for gallstones (GS) (2). Poor understanding of the molecular pathogenesis, aberrant signaling pathways and effect of targeted therapeutic agents on this tumor type has hampered our ability to devise effective strategies to deal with this disease.

Advances in our understanding of activation/deregulation of different signaling pathways in various cancers have resulted in the identification of new drug targets. These aberrant signaling pathways include hedgehog, wnt, notch, TGF-beta pathway etc. The *Hedgehog (Hh)* gene was first discovered by Christiane Nusslein-Volhard and Eric F. Wieschaus in 1980 and the term hedgehog was coined because the mutations in *Hh* gene caused hedgehog like spikes on the cuticle of *Drosophila* larvae (3). Subsequently,

the Hedgehog pathway has been recognised as one of the major regulators of cell growth and differentiation during embryogenesis and early development of vertebrates. Generally, it is inactivated in adults but reactivation via inappropriate mutation or deregulation of this pathway may play a crucial role in tumor development. In addition, Hedgehog pathway is being investigated as a potential therapeutic target for various cancers (4). Many inhibitors of hedgehog pathway have been discovered especially Erivedge (vismodegib) and Odomzo (sonidegib) are the centre of attraction since they have been approved by the U.S. FDA to be used in treatment of basal cell carcinoma.

In vertebrates, the hedgehog pathway consists of Patched receptor (PTCH) that is a membrane protein receptor and Smoothened (SMO) which is a member of 7-transmembrane G protein-coupled receptors family of proteins. In mammals, three families of hedgehog genes exist, namely Indian (Ihh), Desert (Dhh) and Sonic (Shh) hedgehog. Shh is the best-studied ligand of the hedgehog pathway (3). Downstream signaling of SMO in mammals is known as Glioma-associated oncogenes-GLI 1, GLI 2 and GLI 3. GLI 1 is a transcriptional activator (5). Matsushita *et al.* (6) for the first time assessed the status of hedgehog pathway in gallbladder cancer. First, the researchers evaluated the expression of pathway components of sonic hedgehog in GBC tissues and normal gallbladder. They observed the

presence of Gli1 in the nucleus of GBC cells and its absence in normal gallbladder cells. At the same time, enhanced levels of Smoothed (Smo) and Sonic Hh (Shh) were detected in GBC as compared to normal tissue. The GLI has been reported to play a crucial role in development and progression of many cancers. To understand the role of Smo and Shh in GBC oncogenesis, the researchers carried out *in vitro* studies using two GBC cell lines (GBD15 and TGBC2TKB). They turned the “switch off and On” of hedgehog pathway by inhibiting Smo and activating Shh signaling. The inhibition of the effector Smo by Cyclopamine decreased the proliferation and invasiveness of cultured GBC cell lines on the contrary, addition of exogenous recombinant Shh augmented their oncogenic phenotypes. Further, researchers observed that the decrease in GBC cell invasiveness by inhibition of Smo may be as a result of inhibited the epithelial—mesenchymal transition and down expression of MMP-2 and MMP-9. Finally, to check the effect of Smo inhibition on tumor growth, a xenograft model of GBC was used where Smo inhibition by siRNA resulted in the significantly lower size of the tumors than in controls.

To explain the role of hedgehog pathway in carcinogenesis, three mechanisms have been put forward in various types of cancers (5). First, in type 1, the ligand-independent signaling is driven by mutations mainly in PTCH1, PTCH2, SMO and SUFU in the hedgehog pathway component as observed in basal cell carcinoma (BCC) and medulloblastoma. However, based on recent studies using next generation sequencing, this mechanism is unlikely to play a role in GBC oncogenesis (7,8). Whole exome and transcriptome sequencing studies have reported a central role of ERBB pathway in GBC on the basis of somatic mutation profile. Such studies have been carried out with limited number of samples. Therefore, more research is needed with the larger number of cases to comprehensive characterize the somatic mutational landscape and check hedgehog pathway specific mutations in subsets of GBC patients.

Unlike BCC or medulloblastoma, most tumors such as lung, stomach, esophagus, pancreas, prostate, breast, liver and brain also do not harbour recurrent driver somatic mutations in the Hh signaling pathway (9). Rather, these cancers demonstrate activation of ligand-dependent signaling in an autocrine/juxtacrine (type 2) or paracrine (type 3) manner. In the type 2 activation, most of tumors express all the members of hedgehog signaling pathway and require direct hedgehog ligands and may be inhibited

by PTCH 1 antagonistic drugs. To target the type III signaling pathway, there will be requirement of the drugs that control the stromal hedgehog signals though they may not have a complete beneficial therapeutic response as the tumors have variable needs depending on the activation of stromal components induced by hedgehog pathway. Hence, combination therapy is required in these types of cancers.

The findings by Matsushita *et al.* suggest activation of hedgehog pathway in gallbladder cancer and raise the possibility of targeting its components to improve the prognosis in GBC (5). But there are many questions which should be resolved before considering potential drugs/inhibitors and designing therapeutic interventions. First, the findings related to hedgehog pathway in GBC based on classical immunohistochemistry should be validated using alternative modern and robust high-throughput proteomic and genomic approaches. Second, effort should be made to solve the questions which still remain unanswered like whether Hh ligand expression occurs in all the tumor cells or in a small number of tumor stem cells and whether the hedgehog signaling is autocrine or juxtacrine (type 2) or paracrine (type 3) in GBC? Also, targeting a single pathway in cancer may improve prognosis in most of the molecularly recruited patients but after some time the cancer fights back with the help of resistant subclones present in the tumor mass (10). Hence, in addition to hedgehog pathway, it will be important to explore other potential targetable pathways such as wnt, erbb and notch etc. to deal with biological complexities of gallbladder cancer.

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Footnote

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References

1. Wistuba II, Gazdar AF. Gallbladder cancer: lessons from a rare tumour. *Nat Rev Cancer* 2004;4:695-706.
2. Lamarca A, Hubner RA, David Ryder W, et al. Second-line chemotherapy in advanced biliary cancer: a systematic review. *Ann Oncol* 2014;25:2328-38.
3. Varjosalo M, Taipale J. Hedgehog: functions and mechanisms. *Genes Dev* 2008;22:2454-72.
4. Xie J, Bartels CM, Barton SW, et al. Targeting hedgehog signaling in cancer: research and clinical developments. *Onco Targets Ther* 2013;6:1425-35.
5. Gupta S, Takebe N, Lorusso P. Targeting the Hedgehog pathway in cancer. *Ther Adv Med Oncol* 2010;2:237-50.
6. Matsushita S, Onishi H, Nakano K, et al. Hedgehog signaling pathway is a potential therapeutic target for gallbladder cancer. *Cancer Sci* 2014;105:272-80.
7. Li M, Zhang Z, Li X, et al. Whole-exome and targeted gene sequencing of gallbladder carcinoma identifies recurrent mutations in the ErbB pathway. *Nat Genet* 2014;46:872-6.
8. Nakamura H, Arai Y, Totoki Y, et al. Genomic spectra of biliary tract cancer. *Nat Genet* 2015;47:1003-10.
9. Ruch JM, Kim EJ. Hedgehog signaling pathway and cancer therapeutics: progress to date. *Drugs* 2013;73:613-23.
10. McGranahan N, Swanton C. Biological and therapeutic impact of intratumor heterogeneity in cancer evolution. *Cancer Cell* 2015;27:15-26.

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