Future prospect of gallbladder therapy using Hedgehog signaling inhibitor

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Research into Hedgehog (Hh) signaling in gallbladder cancer is in its infancy, and clinical trials are now only being conducted. Importantly, Hh signaling inhibitors work very well *in vitro* and *in vivo* mice models; however, as described by Takebe *et al.* (1), clinical trials of vismodegib, a Smoothened (SMO) inhibitor, has never met the clinical endpoint (2), and thus we must consider this discrepancy.

To account for this anomaly, we must study the tumor microenvironment; in particular, hypoxia. The *in vivo* environment, especially at local tumor sites, exists under hypoxic conditions (3,4). The oxygen tension in local tumor sites is <1.3% O_2 compared with 5.3% in mixed venous blood and 3.3–7.9% in well-vascularized organs (4,5). Therefore, different modes of signaling transduction may occur under hypoxic conditions.

Hh signaling is activated under hypoxic conditions through upregulation of SMO transcription (6). As shown in our previous study (7), inhibition of transcription using siRNA was significantly more effective than suppression of SMO by cyclopamine treatment in gallbladder cancer, demonstrating the importance of its regulation at the transcription level. Many Hh inhibitors are protein or antibody inhibitors, and they may not regulate Hh signaling at the transcriptional level. Under hypoxic conditions, SMO may be constitutively supplied, overwhelming the activity of Hh inhibitors. We believe that analysis of the mechanism of SMO transcription upregulation under hypoxia is seriously required. Recently, it has been shown that transcriptional regulator, recombination signal binding protein for immunoglobulin-kappa-J region (RBPJ), and transcriptional co-activator, mastermind-like 3 (MAML3), contribute to hypoxia-induced upregulation of SMO (8). Such a study may improve the efficacy of Hh inhibitors in clinical use.

As described in Mittal *et al.* (9), whether Hh signaling acts in an autocrine or in a paracrine manner is also an important issue. In addition, we must consider cross-talk signaling. GLI1 is located downstream of Hh signaling as a target gene and transcriptional factor, and therefore, it is a milestone of Hh signaling activation. It has been reported that GLI1 is also activated through other signaling cascades such as the EWS/FLI1 (10), PKC-delta (11), PI3k-AKT (12), and RAS-MEK1 pathways (13), but not through canonical Hh signaling. This infers that SMO inhibition alone is not sufficient to suppress Hh signaling.

GLI2 and GLI3 are also members of the GLI transcription factor family (9). Both occur as inhibitory truncated forms and activated full-length forms. It is difficult for us to discriminate between the two clinically. Previously, we have shown that GLI3 but not GLI1 has a pivotal role in inducing the tumorigenicity of colon cancer (14). Therefore, studies examining the roles of GLI2 and GLI3 in cancer should be conducted in the future.

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Footnote

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