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Editorial

Sonic Hedgehog Signaling, Lipids, and Metabolic Disorders

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The hedgehog (HH) gene was first discovered in Drosophila for its role in embryonic development; however, it plays a crucial and conserved role in numerous processes of vertebrates, such as embryogenesis, epithelial-mesenchymal transition, and cellular development (1-3). Secreted HH ligands can diffuse through the extracellular matrix to act on distant cells (4). In this regard, three homologous ligands for HH have been identified in mammals, including desert (DHH), sonic (SHH), and Indian (IHH) HH ligands (5,6). The interaction of the SHH ligand with the Patched receptor (PTCH1) on recipient cells activates the smoothen (SMO) by relieving its suppression and subsequently activates transcription factors in the glioma-associated oncogene family (7). Recent findings have suggested that there is an interaction between the SHH pathway and other signaling pathways, including Wnt/β-catenin, transforming growth factor β, mammalian target of rapamycin, and notch (8). Evidence implies that the disruption of HH signaling is effectively involved in developing cancers in various organs (9). In this regard, recent studies have revealed that patients with mutations resulting in the impaired activity of SHH signaling effectors Patched and SMO may develop basal-cell carcinomas (10). On the other hand, an impairment in the pathway has been found to cause various metabolic disorders. It has been suggested that impairments in the HH signaling pathways may contribute to several lipid/lysosomal storage disorder diseases, such as Niemann-Pick C 1 and 2 (NPC1, 2) and mucopolysaccharidosis type II (Hunter disease) (10,11).

HH signaling as a morphogen signaling is tightly regulated with unique modifications. The modification of SHH with cholesterol, at the C terminus and palmitate at the N terminus, ensures the SHH trafficking to plasma membranes (12). Lipid modifications also enhance the SHH transporting across the plasma membrane for release extracellularly (13,14). Recent evidence suggests that the lipid moieties attached to SHH play an important role in the interaction between this ligand and the PTCH1 receptor (15). Interactions of the palmitoylated N-terminal of the SHH ligand with PTCH1 are crucial for the inhibition of PTCH1, thus triggering HH signaling via SMO (16). Therefore, inhibiting the PTCH1 receptor on SMO is lost in the presence of cholesterol and 7 -dehydrocholesterol-derived oxysterols (17). However, the biding of synthetic and endogenous oxysterols with the extracellular cysteine-rich domain can allosterically activate SMO (18), and cholesterol as an endogenous activator of SMO can stimulate SHH signaling independently (13). During the SHH signaling, SMO trafficking to the primary cilium is shown to be aided by cholesterol derivatives and oxysterols. This implies the crucial role of cholesterol and other lipids in the activation of the SHH signaling pathway in various organs. Owing to the importance of SHH signaling in metabolic disorders, it seems that cholesterol metabolism might play a critical role in the development of metabolic disorders by the interaction of SHH signaling.

Experimental studies demonstrated that the HH pathway ligand is overexpressed in non-alcoholic steatohepatitis (NASH) specimens. Additionally, it has been reported that the severity of liver disease is directly related to the activity of the SHH pathway in non-alcoholic fatty liver disease (19). However, studies on the liver tissue of patients with simple steatosis revealed that the SHH signaling pathway was downregulated in simple steatosis as compared to NASH-related cirrhosis (20).

Taken together, the possibility of the lipid modification of SHH, PTCH, and SMO, the key signal transducers in the SHH signaling pathway, through different lipid species and cholesterol, might explain why lipid metabolism is associated with an impaired SHH signaling pathway and subsequently their roles in metabolic disorders.

Competing Interests

None.

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Ethical Approval
Not applicable.

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