Lipid Modification of Hedgehog Proteins

Modification of Hedgehog proteins by palmitate and cholesterol

Hedgehog proteins are a family of secreted signaling molecules that play critical roles in development as well as cellular growth and differentiation. The mature Hedgehog (Hh) and Sonic Hedgehog (ShH) proteins are modified by two lipid groups: N-linked palmitate at the amino terminus and a molecule of covalently bound cholesterol at the C-terminus. Our laboratory is studying the enzymology of lipid modification of Hh and ShH proteins both in vivo and in vitro. We have purified Hhat, Hedgehog acyltransferase, a multi-pass membrane protein and shown that Hhat is necessary and sufficient for catalyzing attachment of palmitate to Hedgehog proteins. Our current projects are focused on defining structure/function relationships for Hhat and Shh. We have identified key residues that are important for catalysis within Hhat, and have also defined the minimal region within Shh that is necessary for recognition and palmitoylation by Hhat.

In addition, we are studying the role of Shh in human cancers. Shh is frequently overexpressed in pancreatic cancer, and expression of Shh drives pancreatic tumorigenesis. We reason that inhibition of Hhat, and consequent inhibition of Shh palmitoylation, should block the ability of Shh to mediate pancreatic cancer cell growth. We are currently performing a High Throughput Screen to identify small molecule inhibitors of Hhat, with the hope that these agents will prove to be therapeutically useful.