

SONIC HEDGEHOG SHEDDING RESULTS IN FUNCTIONAL ACTIVATION OF THE SOLUBILIZED MORPHOGEN

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Paracrine Sonic Hedgehog (Shh) signaling is a main determinant of embryonic development and contributes to cancer progression and the maintenance of adult stem cells. The understanding of Shh release and activity, however, has been impeded by its unusual biology. Shh is covalently modified by N- and C-terminal lipidations, which in turn affects numerous aspects of Shh localization, release, movement, and activity. These are only poorly understood. We asked why the sequence of lipid modification, firm attachment to the cell surface, multimerization, and multimer release rather than direct discharge is essential for effective Shh secretion and function, and whether these features are interconnected.

In this presentation, we suggest a new model that integrates multiple controversial and poorly understood features of Shh biology. We found that ADAM-mediated proteolytic shedding of multimeric Shh from the cell surface results in its solubilization in truncated, unlipidated form [1]. In this scenario, Shh N-palmitoylation is the prerequisite for membrane-proximal proteolytic cleavage of an N-terminal peptide during solubilization that otherwise blocks the Shh binding site to its receptor Patched (Ptc) [2], explaining the essential yet indirect role of N-palmitoylation for Shh biological activity. Analysis of the human Shh crystal structure supports this finding, demonstrating that Ptc-binding sites are occupied *in trans* by N-terminal peptides of adjacent morphogens in the cluster. Based on these findings, we present the first structural insight into Shh multimers [3] and provide a new rationale for their formation [4]. We suggest that one of the most striking consequences of Shh release upon N-terminal processing may be the potential conversion of a cell-surface tethered Shh zymogen into a soluble active zinc-metalloprotease [5]. This possibility is supported by the detection of a Shh zinc-coordination site exposed only upon processing of the N-terminal peptides.

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