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CELL SIGNALLING

Releasing a hedgehog

Although Hedgehog proteins can signal to distal cells, they are predominantly tethered to the plasma membrane of expressing cells, by their dual lipid adducts, cholesterol and palmitate. Here, Beachy and colleagues identify a role for SCUBE proteins in the release of lipid-modified Hedgehog proteins.

SCUBE proteins are secreted glycoproteins with nine epidermal growth factor (EGF)-like repeats, a spacer region, a Cys-rich domain and a CUB domain. The authors observed that co-expression of the mammalian Hedgehog homologue, sonic hedgehog (SHH), and SCUBE2 (one of the three mammalian SCUBE proteins) resulted in high levels of active SHH in the supernatant of mammalian cells. Interestingly, the addition of exogenous SCUBE2 was sufficient to increase SHH concentration and activity in the supernatant of SCUBE2-deficient cells, which

Strikingly, SCUBE2 did not increase SHH protein stability but rather the release of dual lipid-modified SHH from the plasma membrane of SHH-expressing cells. Moreover, SCUBE2 mediated the release of cholesterol- and palmitate-modified SHH more efficiently than the release of a cholesterol-modified SHH mutant with defective palmitoylation. The authors also found that SCUBE2 was able to release lipid-modified SHH from lipid rafts (which are detergent-insoluble glycolipid-rich membrane microdomains) *in vitro*. Finally, chromatographic analysis indicated that the released SHH proteins maintained their dual lipid modification.

So, how does SCUBE2 promote SHH release? Although the mechanism was not fully elucidated, SCUBE2-mediated release of SHH was found to be enhanced by SHH palmitoylation and to depend on the expression of Dispatched, a transmembrane protein previously

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the authors show that the spacer region, the Cys-rich and the CUB domains of SCUBE2 are essential for SCUBE2 activity.

Together, these findings shed light on the function of SCUBE proteins and their zebrafish homologues, which were first identified 17 years ago in Hedgehog signalling-deficient mutants. Moreover, they reveal a mechanism that enables lipid-modified Hedgehog proteins to signal at distal sites.

Maria Papatriantafyllou

ORIGINAL RESEARCH PAPER Creanga, A. *et al.*