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Dispatched protein releases Hedgehog from cells

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Abstract

A novel *Drosophila* segment polarity gene is identified and shown to be required for release of Hedgehog protein from secreting cells.

Significance and context

Hedgehog (Hh) proteins are evolutionarily conserved signaling molecules that can act over several cell diameters and are implicated in a range of developmental processes. They are synthesized as precursor proteins that are secreted and undergo autoproteolytic cleavage to generate a biologically active amino-terminal fragment (Hh-N). Concomitant with cleavage, a cholesterol moiety is added to the carboxyl terminus of Hh-N that allows it to bind to cell membranes and restricts its range of action. Diffusion of Hh-N is further restricted by sequestration by its receptor, Patched (Ptc). The presence of the cholesterol anchor on Hh-N raises the question of how it is released from signaling cells. Burke *et al*. show that the product of the *dispatched* gene is a protein with a sterol-sensing domain; this protein releases Hh-N from signaling cells.

Key results

To identify additional genes acting in the Hh signaling pathway, a collection of P-element-induced lethal mutations on the third chromosome was screened for *hedgehog* (*hh*)-like phenotypes. One such mutation (*l(3)S03770*) was named *dispatched* (*disp*) and, by clonal analysis in the adult wing, shown to be specific for the Hh pathway. The *disp* gene was cloned by virtue of the P-element insertion, cDNAs were isolated and the nucleotide sequence determined. The predicted protein of 1,218 amino acids has 12 putative transmembrane domains and shows some similarity to *Drosophila* and vertebrate Ptc and Niemann-Pick type C (NPC1) proteins in a putative sterol-sensing domain (SSD). Outside this region similarity is weak, and the authors suggest that Disp, along with a *Caenorhabditis elegans* Disp homolog, represents a new family of SSD-containing proteins. Further clonal analysis in wing imaginal discs showed that Disp functions only in Hh-secreting cells and plays no part in transducing the Hh signal, despite its similarity to Ptc. Fully processed Hh-N is observed in *disp* homozygotes, demonstrating that Disp has no role in proteolytic cleavage. Levels of Hh protein were, however, greatly increased in $disp^{-}/disp^{-}$ cells, with a concomitant decrease in receiving cells, indicating that Hh is being

retained in the mutant. This retention is dependent on the cholesterol moiety, as Hh-N lacking cholesterol was not retained in *disp*$^{-}$/*disp*$^{-}$ cells.

Links

The GenBank accession number for *disp* is AF200691. The interactive fly has information on *Drosophila* Hedgehog and its vertebrate counterparts.

Conclusions

Burke *et al*. make the intriguing observation that both sequestration of Hedgehog (by Ptc) and release (by Disp) involve proteins with SSDs and require the cholesterol modification of Hh-N so that, despite their inverse roles, these proteins may share a common mechanism.

Reporter's comments

This paper reports a new function for the Dispatched protein in the specific release of a cholesterol-modified protein from cell membranes. The precise mechanism by which it achieves this, and the role of the SSD remain, however, unexplained. The authors suggest a number of possibilities, but a detailed biochemical analysis is required to resolve the issue.

Table of links

Cell

GenBank

The interactive fly

References

1. Burke R, Nellen D, Bellotto M, Hafen E, Senti KA, Dickson BJ, Basler K: Dispatched, a novel sterol-sensing domain protein dedicated to the release of cholesterol-modified Hedgehog from signaling cells. Cell. 1999, 99: 803-815. 0092-1903