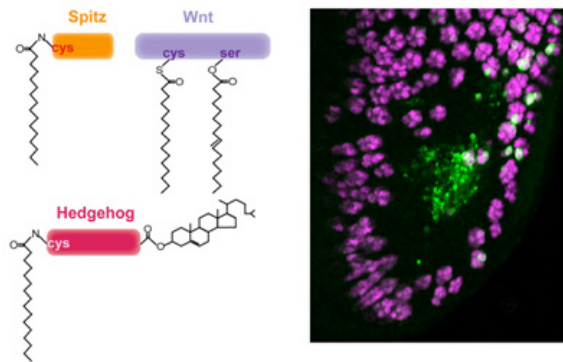


During development, cell-cell signaling allows cells to determine their position in the organism, to take on appropriate fates, and to form contacts with the correct partners. We are studying these processes using the visual system of the fruit fly *Drosophila* as our primary model. The repetitive, yet exquisitely organized structure of the *Drosophila* eye and the power of unbiased genetic screens have allowed us to uncover general mechanisms by which cells communicate.

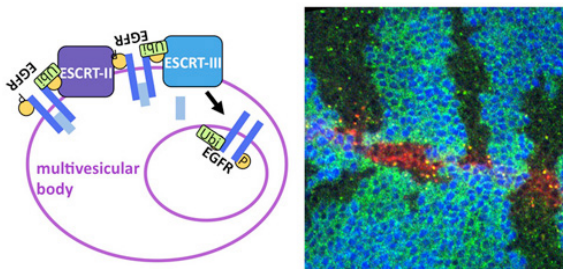
Movement of signaling molecules between cells

Signaling proteins must convey information between cells by traveling in the extracellular space. Surprisingly, we discovered that both the Hedgehog and Spitz signaling molecules are modified with fatty acids by the same enzyme, Rasp, and that these modifications are essential for their function. How can hydrophobic modifications enhance the function of diffusible molecules? For Spitz, the answer seems to be that the fatty acid restricts its diffusion, allowing enough Spitz to build up close to the source to activate the receptor on nearby cells. We are still investigating how lipid-modified proteins can be released to act over a longer range. We also want to know whether this mechanism is used to regulate the activity of other classes of signaling proteins.



Signal transduction

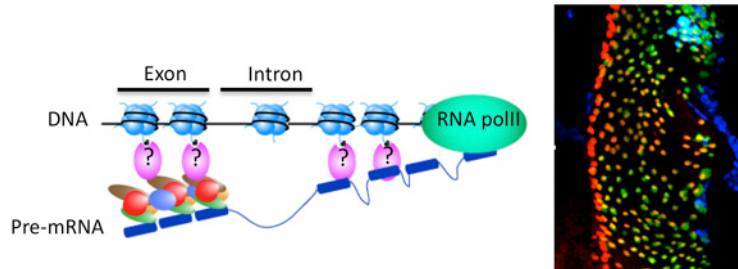
Receptor activation triggers a complex cascade of events that ultimately result in a cellular response. These events may be compartmentalized within the cell. The epidermal growth factor receptor (EGFR) is endocytosed and eventually degraded when it binds its ligand Spitz. We have found mutations that interrupt this endocytic process and also reduce EGFR signaling, suggesting that signaling may occur on endosomes rather than at the plasma membrane. One consequence of endocytosis is proteolytic cleavage of the receptor; we are testing whether the cleaved cytoplasmic domain can function in parallel to the canonical downstream signaling pathway.



Gene expression

The ultimate output of cell-cell signaling is changes in gene expression. Transcriptional activation and repression require not only sequence-specific transcription factors, but also more general complexes that alter chromatin structure or recruit the basal transcriptional machinery. We have found that some subunits of such complexes act as adaptors that allow them to

contribute to transcriptional regulation by specific signal transduction pathways. Gene expression can also be regulated post-transcriptionally. We recently showed that the exon junction complex plays a role in splicing a limited subset of transcripts that includes *MAP kinase*, a critical signal transduction component. MAP kinase and many other genes regulated by this mechanism are located in heterochromatin, raising the intriguing possibility of a connection between chromatin structure and splicing.



Synapse formation

Establishment of the correct neural circuitry requires growing axons to recognize the appropriate cells as synaptic partners. The photoreceptors that mediate color vision provide us with a simple system in which to examine this process. We have found that the receptor tyrosine phosphatase LAR is required for ultraviolet-sensitive photoreceptors to form synapses with the correct partners, and that it signals by a novel mechanism in this process. We are interested in understanding the pathway upstream and downstream of LAR, and also in identifying other molecules that provide targeting information to the color photoreceptors. We are also beginning to study axon regeneration in the visual system.

