CDB SEMINAR

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Thursday, August 31

16:00~17:00 C1F CDB Auditorium

Regulation of Cubitus interruptus, the transcription factor on the Hedgehog signal transduction pathway

Summary

The Hedgehog (Hh) signalling pathway is involved in patterning and organogenesis during the development of many organisms. Mutations in the pathway cause developmental abnormalities, and inappropriate activation of the pathway in adults can lead to initiation and/or maintenance of many types of cancer.

The effects of Hh signalling are mediated by Gli/Cubitus interruptus (Ci) transcription factors. In the absence of the ligand Hh, Ci is cleaved to a shorter form that represses some Hh-target genes. When Hh signals, proteolysis is inhibited and full-length Ci becomes further activated, leading to Hh-target gene expression.

I will present the results of two projects in my laboratory on the mechanism of Ci proteolysis. I (and others) have shown that phosphorylation of Ci by three kinases (Protein Kinase A (PKA), Glycogen Synthase Kinase 3 (GSK3), and Casein Kinase I (CKI)) is required for its limited proteolysis, though the role for CKI is less firmly established. I have made heritable, inducible RNA interference (RNAi) constructs to examine the roles of the eight *Drosophila* CKI family members *in vivo*. I find that, in contrast to published reports from *Drosophila* clone 8 cells, CKIα and CKIε/Doubletime act redundantly in Ci processing. CKI also has a negative role in Wnt signalling: it phosphorylates Armadillo/β-catenin, leading to its degradation in the absence of Wnt signal. I have used my RNAi constructs to determine which CKI isoforms are involved in Wnt signalling.

The ubiquitin proteasome pathway has been implicated in the proteolysis of Ci, which, unusually, leaves part of the Ci molecule intact. I will present the results of Yifei Wang, a graduate student in my lab, on a structure-function analysis on Ci and his efforts to distinguish between several competing models for partial degradation by the proteasome. Yifei has identified novel domains of Ci that are required for its proteolysis, including a possible ubiquitination site. His results thus far are consistent with the endoproteolytic cleavage of Ci by the proteasome.

Host:

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