CDB SEMINAR

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17:00~18:00 Seminar Room A7F

Pervasive translational regulation of the cell signaling circuitry underlies mammalian development

Summary

Both the degree and dynamics of translational control during mammalian development remain poorly understood. There is a lack of understanding for how translational control may drive key cell fate decisions, contribute to complex body plan formation, and underlie evolutionary diversity. We monitored translation of the mammalian genome as cells become specified and organize into tissues in vivo. This identified unexpected and pervasive translational regulation of most of the core signaling circuitry including Shh, Wnt, Hippo, PI3K and MAPK pathways, revealing a new layer of control to major signaling networks. We further show in cis and trans the impact of this translational regulation on cell signaling and tissue patterning. Our results identify a complex landscape of upstream open reading frames (uORFs) across the 5'UTRs of key signaling components, including multiple components of the Shh and Hippo pathways. Focusing on the Shh signaling pathway as a paradigm example, we functionally demonstrate the importance of uORF-mediated translational repression of the major SHH receptor Ptch1 mRNA translation in control of cell signaling and neuronal differentiation. We further identify that Eif3c, a single subunit of the essential 13-subunit eukaryotic initiation factor 3 translation initiation complex, is a critical translational regulator of Ptch1 mRNA translation. We find that Eif3c haploinsufficient mice show striking Shh-dependent tissue patterning defects in vivo. Finally, we show that translation diversifies gene expression spatially across developing tissues whereby hundreds of mRNAs, underlying critical tissue-specific developmental processes, are regulated at the level of translation without changing at the transcript level, at the same stage of embryonic development. Together, this work unravels that a key designing principle of translational control in mammals is to modulate the expression of the core signaling circuitry that is vital for accurate tissue patterning and controlled, at least in part, by the functional specialization of perceived housekeeping translation initiation machinery.

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