SBMC 2010 Conference on Systems Biology of Mammalian Cells
June 3rd-5th 2010 · Freiburg | Germany · Konzerthaus · www.sbmc2010.de

TRANSCRIPTIONAL FEEDBACK REGULATION OF SIGNAL TRANSDUCTION

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Cell fate decisions typically require ongoing activation of upstream signalling pathways for many hours. By analyzing published gene expression profiles we were able to show that virtually all mammalian signal transduction pathways induce their own inhibitors at the transcriptional level (Mol. Syst. Biol. 4, 190). This suggests that transcriptional negative feedback is a general design principle for modulating the long-term signalling dynamics and thus cell fate decisions. Using a reverse engineering approach, we could demonstrate that transcription factor knockdowns mostly enhance upstream signal transduction, further confirming the functional relevance of transcriptional negative feedback. By focusing on TGFβ signalling in primary mouse hepatocytes, we showed that a systems biological approach including array-based identification of potential feedback regulators, Western Blot measurements of protein dynamics and mechanistic modeling of TGFβ/Smad signalling could successfully identify the onco-protein SnoN as the major feedback regulator of the system. Finally, I will briefly present recent work showing that transcriptional negative feedback regulation of BMP signalling during Xenopus development is important for proper morphogen gradient interpretation and for suppression of embryo-to-embryo variability.