CDB SEMINAR

Pablo Wappner

Instituto Leloir, Buenos Aires, Argentina

Friday, June 10, 2011
16:00~17:00 A7F Seminar Room

Genome-wide RNAi screen identifies novel genes required for the response to hypoxia

Summary

The Hypoxia Inducible Factor (HIF) is an alpha-beta heterodimeric transcription factor composed of two helix-loop-helix-PAS (bHLH-PAS) subunits. It is regulated mainly at the level of oxygen-dependent protein stability of its alpha subunit. Whereas in normoxia HIF-alpha is rapidly degraded at the 26S proteasome, in hypoxia the protein is stabilized, and accumulates in the nucleus.

We have previously shown that the *Drosophila* HIF homologue Sima plays a central role in the sprouting response of the tracheal system in conditions of oxygen deprivation. We have now conducted an unbiased genome-wide RNAi screen in *Drosophila* cells aimed to the identification of novel genes involved in HIF/Sima regulation. After 3 rounds of selection, 35 genes emerged as critical regulators of HIF activity in hypoxia, most of which had not been previously associated to HIF biology. We focused our analysis on components of chromatin remodeling complexes, including Reptin, Pontin and Moira, and the miRNA pathway component Argonaute 1. We have validated the requirement of these genes for the activation of a HIF inducible reporter in transgenic flies, and by assessing the expression of Sima target genes in embryos. Studies carried out both in cell culture and *in vivo* confirmed the physiological requirement of Argonaute 1 and the miRNA machinery for HIF dependent transcription, as well as a role of Pontin and Reptin in HIF dependent transcription through the modification of chromatin structure at HIF-responsive promoters.

Host:
Shigeo Hayashi
Morphogenetic Signaling, CDB
shayashi@cdb.riken.jp
Tel:078-306-3185 (ext:1523)