Scientists discover Par-1 as a new component of the Hippo signaling pathway

August 6 2013

In the development of animals, which is closely controlled by diverse pathways, the regulation of organ size has been a long-standing puzzle. How does an organ ascertain its optimum size? What are the molecular mechanisms that stop organ growth at an appropriate point during development or regeneration? Almost a decade ago, the discovery of the Hippo signaling pathway provided an important starting point for answering these questions.

Now, a team of scientists led by Lei Zhang at the Shanghai Institute of Biochemistry & Cell Biology, Chinese Academy of Sciences, has identified a novel component of this pathway, which influences the Hippo protein's phosphorylation status and Hippo-Salvador (another key component of this pathway) association to negatively regulate Hippo kinase activity. Their findings will be published in the open access journal *PLOS Biology*.

The Hippo pathway regulates organ growth by controlling cell numbers in that organ through the inhibition of the transcriptional coactivator, Yorkie, by a series of phosphorylation events. To initiate these phosphorylation events, the Hippo kinase needs to be phosphorylated on the Thr195 site. Without inhibition from Hippo signaling, Yorkie translocates into the nucleus to bind with transcription factors to induce the expression of specific genes that promote proliferation and inhibit apoptosis. Extensive research has been focused on the study of inappropriate overgrowth induced by Yorkie activity, which is believed to be related to human cancers.

However, the mechanisms that restrict Hippo kinase activity, which results in increased apoptosis and reduced tissue growth, remain unclear. In particular, the identity of the kinase that antagonizes Hippo remains unknown. To help elucidate these mechanisms, the Zhang group performed a gain-of-function screen in Drosophila melanogaster to identify the negative regulators of the Hippo pathway. After screening more than 10,000 lines, they found that Par-1, a multifunctional serine/threonine kinase, promotes organ growth by affecting the Hippo signaling pathway.

Dr. Lei Zhang and his colleagues demonstrated that Par-1 physically interacts with Hippo and its scaffold protein, Salvador. Using biochemical approaches, they were able to show that Par-1 regulates the phosphorylation of Hippo at Ser30 and promotes the dissociation of Salvador from the Hippo-Salvador complex, eventually resulting in Salvador dephosphorylation and destabilization. "How the activity of Hippo is regulated is fascinating to all scientists in this field. Our studies provide the first-hand evidence that, besides the well-known Thr195 autophosphorylation site, Hippo's activity can be affected by another phosphorylation site," said first author Hongling Huang.

"With this new understanding of how Par-1 regulates Hippo activity and prevents inappropriate Hippo activation, our knowledge of the Hippo signaling network has greatly expanded. As the function of Par-1 in regulating Hippo signaling is evolutionarily conserved, our studies also suggest Par-1 plays a role in carcinogenesis," added Dr. Lei Zhang. "Considering that Par-1 is a well-known polarity regulator, we'd like to focus on exploring the relationship between the Hippo pathway and the polarity components in the future."

More information: Huang H-L, Wang S, Yin M-X, Dong L, Wang C, et al. (2013) Par-1 Regulates Tissue Growth by Influencing Hippo Phosphorylation Status and Hippo- Salvador Association. *PLoS Biol*

11(8): e1001620. doi:10.1371/journal.pbio.1001620