

Axin is a master scaffold for multiple signaling pathways



Department of Biological Sciences
Seminar Announcement

Date: Friday, 21 August 2009
Time: 4pm
Venue: LT 20
Host: Prof Hew Choy Leong

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It is well established that Axin is a major scaffold for the beta-catenin degradation complex in resting cells. However, Axin has also emerged as a scaffold for multiple other signaling cascades, including the pathways for JNK MAPK, TGF-beta, mTOR, and p53 signaling. We found that Axin can interact with MEKK1 or MEKK4 to stimulate the JNK MAP kinase via MKK4/7. Using zebrafish as a model system, we found that Axin/JNK signaling is involved in beta-catenin-independent dorsalization during embryonic development. Recently, we have revealed a surprising role of Axin in determining cell fates upon DNA damage. Although many factors have been known to exert roles in cellular commitment to undergo cell arrest or apoptosis following genotoxic stresses, how they are orchestrated to selectively reach respective thresholds remains unclear. We have found that Axin plays a scaffolding role for HIPK2, p53, Pirh2 and Tip60, forming distinct complexes in cellular commitment to cell-cycle arrest or apoptosis. In sublethally damaged cells, Pirh2 strongly abrogates Axin-based genotoxic induction of p53 Ser-46 phosphorylation by HIPK2 by excluding HIPK2 from association with the Axin/p53 complex, rendering the Axin-bound p53 underphosphorylated at Ser-46. Pirh2-Axin interaction is disrupted by binding of Axin to Tip60 in apoptotic cells upon lethal treatment. Thus, we have identified distinct complexes that control the levels of p53 activation to trigger cell-cycle arrest or apoptosis upon different severity of genotoxic stress. Mutation in AxinFu mice promotes tumorigenesis following DMBA treatment, further emphasizing the importance of Axin in tumor suppression.

