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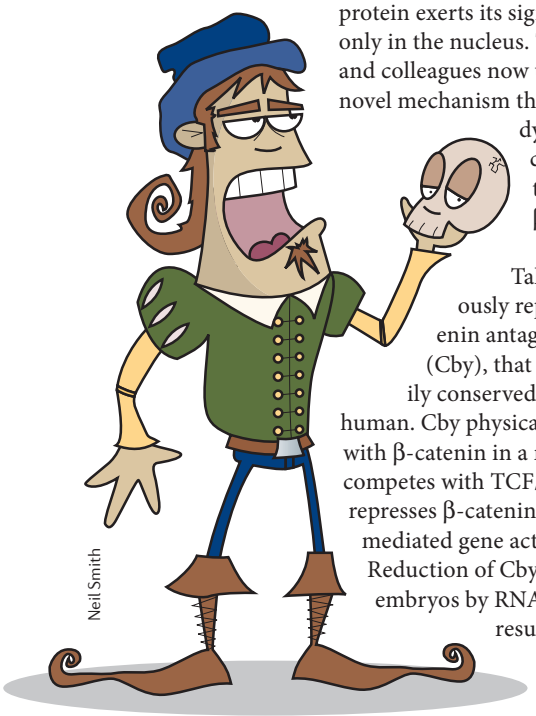
CELL SIGNALLING

AKTing in Wnt pathway

> …highlights the complex nature of the crosstalk between Wnt and AKT/PKB signalling pathways.

The Wnt–β-catenin pathway is pivotal for numerous important cellular events during embryonic development, tissue homeostasis and tumorigenesis. β-catenin enters the nucleus following Wnt stimulation, and acts as a transcriptional coactivator by binding to T-cell factor/lymphoid enhancer factor (TCF/LEF). Nuclear import and export of β-catenin represents a crucial step in regulating signalling-competent β-catenin levels, as this protein exerts its signalling activity only in the nucleus. Takemaru and colleagues now unravel a novel mechanism that controls the dynamic nucleo–cytoplasmic trafficking of β-catenin.



Neil Smith

The group of Takemaru previously reported a β-catenin antagonist, Chibby (Cby), that is evolutionarily conserved from fly to human. Cby physically interacts with β-catenin in a manner that competes with TCF/LEF, and thus represses β-catenin-mediated gene activation. Reduction of Cby levels in fly embryos by RNA interference results in hyperactivation of this pathway, which highlights the biological importance of the function of Cby.

To further elucidate the molecular and cellular functions of Cby, Takemaru and colleagues isolated Cby-binding partners. Using affinity purification-mass spectrometry, they identified 14-3-3ε and 14-3-3ζ as novel Cby interactors. 14-3-3 proteins that bind to a multitude of functionally diverse signalling proteins specifically recognized Ser20 within the N-terminal 14-3-3-binding consensus motif of Cby. This interaction requires the phosphorylation of this critical Ser residue by AKT/protein kinase B (PKB), as a kinase-dead AKT/PKB mutant almost completely abrogated the binding of 14-3-3 proteins to Cby. Wild-type Cby either localized to the cytoplasm or to both the nucleus and the cytoplasm, whereas Cby mutants defective in 14-3-3 binding preferentially localized to the nucleus. These findings indicate that association with 14-3-3 triggers the sequestration of Cby to the cytoplasm.

The authors then showed that Cby and 14-3-3 form a trimolecular complex with β-catenin in tissue culture cells. Intriguingly, Cby and 14-3-3 collaborate to promote cytoplasmic localization of β-catenin and thereby inhibit β-catenin signalling. An Ala substitution for Ser20 in Cby eliminated binding to 14-3-3 and partially compromised the ability of Cby to inhibit β-catenin signalling.

Several lines of evidence indicate that AKT/PKB has a positive role in Wnt–β-catenin signalling. This study provides evidence that nuclear-targeted AKT/PKB inhibits, whereas membrane-tethered AKT/PKB stimulates, β-catenin-mediated transcriptional activation. It is possible that membrane and cytoplasmic AKT/PKB favourably phosphorylates and thus inactivates glycogen synthase kinase-3, whereas nuclear AKT/PKB phosphorylates β-catenin and Cby. In turn this facilitates 14-3-3 binding and the subsequent nuclear exclusion of the ternary complex. Therefore, the subcellular compartmentalization of AKT/PKB differentially influences β-catenin signalling. This finding highlights the complex nature of the crosstalk between Wnt and AKT/PKB signalling pathways.

Taken together, these data suggest a novel paradigm through which Cby acts, in concert with 14-3-3 proteins, to facilitate nuclear export of β-catenin and thereby antagonize β-catenin signalling. The authors propose that inhibition of β-catenin signalling by Cby involves at least two distinct molecular mechanisms: competing with TCF/LEF transcription factors for β-catenin in the nucleus and facilitating nuclear export of β-catenin through interaction with 14-3-3 following its phosphorylation by AKT/PKB.

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ORIGINAL RESEARCH PAPER Li, F.-Q. *et al.* Chibby cooperates with 14-3-3 to regulate β-catenin subcellular distribution and signaling activity. *J. Cell Biol.* **181,** 1141–1154 (2008)