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Targeting Akt regulatory mechanisms for cancer therapy

Pengda Liu
The University of North Carolina, USA

Hyperactivation of the PI3K-Akt pathway is observed in virtually all solid tumors. Multiple genetic events such as PTEN loss and PIK3CA amplification partially account for the increase in the pathway activation. In addition to genetic changes, dysregulation of post-translational modifications of Akt, including phosphorylation, acetylation, hydroxylation, methylation and others, that are necessary for Akt activation is also frequently observed in various types of cancers. However, whether and how Akt is regulated by its binding partners are minimally understood. To this end, through a proteomic approach, we have identified the tumor suppressor SAV1 as a novel Akt interacting partner to suppress Akt activation. Furthermore, we found that phosphorylaton of Akt1-Y26 disrupts SAV1 binding and subsequently activate Akt, which is large mediated by TAM kinases. Mechanistically, TAM-mediated Akt1-Y26 phosphorylation facilitates Akt plasma membrane recruitment by PI(3,4,5)P3 to promote Akt activation. On the other hand, TAM inhibition leads to enhanced SAV1 binding and reduced Akt activity. Importantly, cancer patient-derived SAV1 mutants and Akt1 mutants were identified to exert elevated oncogenicity by bypassing SAV1 binding and suppression, further supporting a pathophysiological role of the identified TAM/Akt/SAV1 signaling in tumorigenesis and the potential to target this Akt regulatory axis for inhibition to combat cancer.

Biography

Pengda Liu has completed his PhD from East Carolina University and Post-doctoral studies from Duke University Medical Center and BIDMC, Harvard Medical School. He is currently an Assistant Professor in the Department of Biochemistry and Biophysics at UNC-Chapel Hill. He has published more than 38 papers in peer-reviewed journals and has been serving as an ad hoc reviwers for many reputed journals.

pengda_liu@med.unc.edu

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