Akt hyperphosphorylation by Akt-specific inhibitor

Khan Mohammad Golam Maola

Akt, a member of the serine/threonine protein kinase, is a positive regulator of growth factor signaling processes including proliferation and survival. A-443654 is an ATP-competitive nonspecific Akt inhibitor. Based on the A-443654 they designed and synthesized two Akt-specific inhibitor, PrIDZ and 3-IB-PP1. They designed the inhibitors by using the combination of an analog sensitive (as) kinase allele with an as allele–specific inhibitor. They explored that PrIDZ and 3-IB-PP1 induce hyperphosphorylation of Akt in a dose-dependent and ATP-competitive manner. They also found that the Akt hyperphosphorylation is induced by kinase-intrinsic model, in which inhibitor binding to the ATP site triggers hyperphosphorylation.

Article

Inhibitor hijacking of Akt activation

Tatsuya Okuzumi, Dorothea Fiedler, Chao Zhang, Daniel C Gray, Brian Aizenstein, Randy Hoffman & Kevan M Shokat
(University of California, San Francisco, California, USA)
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Summary: The kinase Akt plays a central role as a regulator of multiple growth factor input signals, thus making it an attractive anticancer drug target. A-443654 is an ATP-competitive Akt inhibitor. Unexpectedly, treatment of cells with A-443654 causes paradoxical hyperphosphorylation of Akt at its two regulatory sites (Thr308 and Ser473). We explored whether inhibitor-induced hyperphosphorylation of Akt by A-443654 is a consequence of disrupted feedback regulation at a pathway level or whether it is a direct consequence of inhibitor binding to the ATP binding site of Akt. Catalytically inactive mutants of Akt revealed that binding of an inhibitor to the ATP site of Akt is sufficient to directly cause hyperphosphorylation of the kinase in the absence of any pathway feedback effects. We conclude that ATP-competitive Akt inhibitors impart regulatory phosphorylation of their target kinase Akt. These results provide new insights into both natural regulation of Akt activation and Akt inhibitors entering the clinic.

Reference

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