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Nuclear-cytoplasmic shuttling of p21$^{Cip1/WAF1}$ is regulated by Akt

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Cellular models, Pathogenesis and cell biology

Context

The serine-threonine kinase Akt is a central component of signaling pathways controlling both cellular proliferation and apoptosis. In previous studies the authors showed that overexpression of HER-2/*neu*, a membrane tyrosine kinase whose upregulation correlates with some breast and ovarian cancers, activates signaling through Akt in NIH3T3 cells. By studying the cellular and molecular consequences of Akt activation in the context of these HER-2/*neu* overexpressing cells, the authors set out to reveal fundamental information regarding the signaling mechanisms altered during malignant progression.

Significant findings

Akt activation induces cellular proliferation, but does not alter apoptotic events. Akt interacts with the cell cycle inhibitor $p21^{Cip1/WAF1}$ and phosphorylates a threonine residue that resides in the molecule's carboxy-terminal nuclear localization sequence (NLS). Total levels of $p21^{Cip1/WAF1}$ were not altered by Akt activation, but its subcellular distribution was altered: when $p21^{Cip1/WAF1}$ NLS phosphorylation is reduced the protein is predominantly nuclear, but when $p21^{Cip1/WAF1}$ is phosphorylated it is cytoplasmic. Collectively these findings suggest a model in which cell proliferation can be influenced by HER-2/*neu*-Akt signaling pathways by altering the subcellular localization of specific cell cycle regulators. In this case, activated Akt phosphorylates the cell-cycle inhibitor $p21^{Cip1/WAF1}$, thereby causing it to shuttle to the cytoplasm where it is sequestered from its targets in the nuclear cell cycle machinery.

Comments

This paper has contributed significantly to our understanding of the molecular underpinning of HER-2 signaling mechanisms. Moreover, the finding that Akt regulates $p21^{Cip1/WAF1}$ activity by directing its subcellular localization uncovers a clever regulatory mechanism that is likely to be employed in other signaling contexts. These results underscore the possibility of developing therapies to activate (or inactivate) cell cycle regulators by altering their subcellular localization.

The authors' conclusions would be strengthened by a demonstration that (in the context of wild-type, endogenous HER-2/neu) endogenous cytoplasmic $p21^{Cip1/WAF1}$ is phosphorylated whereas the nuclear fraction of the protein is unphosphorylated. The future development of phosphospecific $p21^{Cip1/WAF1}$ antibodies would significantly clarify the phosphorylation status of endogenous pools of $p21^{Cip1/WAF1}$ in the cell types utilized here and in other cell types as well.

Methods

Cell proliferation assays, phosphoaminoacid analysis, coimmunoprecipitation, immunoblotting, transient transfections, immunofluorescence, colony-formation assay, cellular fractionation (cytosol/nucleus), BrdU incorporation.

Additional information

References

1. Zhou BP, Liao Y, Xia W, Spohn B, Lee M-H, Hung MC: Cytoplasmic localization of $p21^{Cip1/WAF1}$ by AKT-induced phosphorylation in HER-2/neu-overexpressing cells. Nat Cell Biol . 2001, 3: 245-252.