Viewpoint

p27^{KIP1} phosphorylation by PKB/Akt leads to poor breast cancer prognosis

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Introduction

Three papers published concurrently in the October issue of *Nature Medicine* have demonstrated new links between mitogenic cytokine signalling and the cell cycle inhibitor p27^{KIP1}, and have elucidated how this link may contribute to breast cancer patient prognosis [1–3].

Cell cycle control occurs through cyclin binding to the cyclin-dependent kinases (CDKs) that stimulate G1 progression [4]. p27^{KIP1} is a member of the kinase inhibitor protein (KIP) family that inhibit cell cycle progression by binding to cyclin-CDK complexes [5]. In cancers where protein kinase B (PKB)/Akt is constitutively activated by upstream oncogenes, Akt decreases p27^{KIP1} by increasing proteolysis and reducing transcription [6].

These three articles describe a third way in which Akt resists G1 arrest, namely by a p27^{KIP1} phosphorylation that impairs nuclear import and prevents its inhibition of cyclin-CDK complexes. The authors of these studies conclude that exclusion of p27^{KIP1} from the nucleus leads to a poor patient outcome in breast cancer [1-3].

p27^{KIP1} phosphorylation leads to cytoplasmic localisation

Wild type and constitutively active Akt were both shown to phosphorylate p27^{KIP1} at threonine157, leading to cytoplasmic localisation of p27^{KIP1}. Blockade of Akt activation by the phosphatidyl inositol 3′-kinase (PI3K) inhibitor LY294002, or transfection with the mutant p27^{KIP1}-T157A, led to nuclear p27^{KIP1} localisation. Constitutively active Akt prevented wild type p27^{KIP1}, but not p27^{KIP1}-T157A, from causing G1 arrest.

In two of the studies it was reported that approximately 40% of primary breast tumours displayed cytoplasmic p27^{KIP1} staining [1,3]. The presence of cytoplasmic p27^{KIP1} in human breast cancers was highly correlated with Akt activation. The best prognostic subgroup of breast tumours had strong, exclusively nuclear p27^{KIP1} staining, while cancers with lower expression levels, but cytoplasmic localisation, had the worst survival rates.

The data indicate that p27^{KIP1} normally acts as a tumour suppressor protein, but that the oncogenic activation of Akt leads to mislocation of p27^{KIP1} to the cytoplasm where it is unable to inhibit cell cycle proteins. The study indicates that cytoplasmic location of p27^{KIP1} in breast tumours is a prognostic indicator and that the Akt pathway may be a good target for anti-cancer therapy.

Conclusion

p27^{KIP1} is an inhibitor of cell cycle progression that is rarely mutated or silenced in cancers. The *Nature Medicine* articles demonstrate that p27^{KIP1} depends on a nuclear location to perform its cell cycle inhibitory function and that Akt phosphorylates p27^{KIP1} leading to its mislocalisation in the cytoplasm [1–3].

Akt lies downstream of PI3K and the growth factor receptors epidermal growth factor receptor (EGFR) and ErbB2, which act as oncogenes in numerous cancers [7]. This means that Akt is commonly activated in many forms of cancer [8]. All three of these studies confirm that the action of Akt on p27^{KIP1} localisation appears crucial to breast tumour progression [1–3]. There is evidence that Akt can also exclude nuclear presence of another cell cycle inhibitor, p21^{CIP1} [9]. It will be interesting to see whether the cellular location of p21^{CIP1} will add to the prognostic information given by p27^{KIP1} in cancers.

Finally, the articles suggest new therapeutic opportunities in targeting Akt or the p27^{KIP1} phosphorylation site to relocate p27^{KIP1} to the nucleus and improve the long-term

CDK = cyclin-dependant kinase; KIP = kinase inhibitor protein; PKB = protein kinase B; PI3K = phosphatidyl inositol 3′-kinase.

prognosis of breast cancer patients in whom this important cell cycle regulator is mislocated.

Competing interests

None declared.

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