Participation of cyclin D1 deregulation in TNP-470-mediated cytostatic effect: involvement of senescence

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摘要

Abstract

Inhibition of angiogenesis is becoming one promising, alternative approach to stop tumor from growth and spreading to distant organs. TNP-470, an analog of fumagillin, possesses potent anti-angiogenic effects with minimal toxicity in animal tumor models and is now in the phase III of human cancer trial. Although TNP-470 induced endothelial cell cycle arrest at G1 phase via p53 and p21(Cip1), the underlying mechanism of the cytostatic effect of TNP-470 on endothelial cells remains limited. We have found that TNP-470 did not only induce p53 and p21(Cip1) but also cyclin D1 in the basic fibroblast growth factors (bFGF)-treated endothelial cells. The TNP-470-mediated increase of cyclin D1 protein was due to the enhanced expression of mRNA. Theinduced cyclin D1 formed a complex with cyclin-dependent kinase4 (CDK4) and p21(Cip1). The ability of cyclin D1-associated CDK4 to phosphorylate retinoblastoma (Rb) protein was, however, reduced in the same cells. TNP-470 also significantly increasedsenescence-associated-beta-galactosidase activity (SA-gal), hallmark of cells undergoing senescence. Interestingly, the effect of increased cyclin D1 protein mimicked by overexpression of cyclin D1 increased the sensitivity of human umbilical vein endothelial cells (HUVECs) to TNP-470. In summary, the cytostatic effect of TNP-470 on endothelial cells is in part mediated by induction of senescence and cyclin D1 is a key molecule participating in this event.