Inhibition of Human Vascular Endothelial Cells Proliferation by YC-1 Through a cyclic GMP-Independent Pathway

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摘要

Abstract

This study was designed to investigate the effect of YC-1, 3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole, in human umbilical vein endothelial cells (HUVECs) proliferation and its underlying mechanism. YC-1 at a range of concentrations (5-50 μM) inhibited DNA synthesis and decreased cell number in cultured HUVEC in a dose- and time-dependent manner. YC-1 was not cytotoxic at these concentrations. [3H]thymidine incorporation and flow cytometry analyses revealed that YC-1 treatment decreased DNA synthesis and arrested the cells at the G0/G phase of the cell cycle. Western blot analysis demonstrated that YC-1(5-50 μM) increased the levels of cyclin-dependent kinase (CDK)-inhibitory proteins (CKIs), p21 and p27, but did not induce any significant changes of cyclins and CDKs. In the YC-1-treated HUVEC, the formation of CDK2-p21 complex, but not CDK2-p27 complex, was increased and the assayable CDK2 kinase activity was decreased. These changes were in a dose-dependent manner. In contrast, the formations of CDK4-p21 and CDK4-p27 complex were slightly increased and the assayable CDK4 kinase activity was slightly decreased (if there were any changes). Pretreatment with guanylyl cyclase inhibitors, 1H-(1,2,4)oxadiazolo[4,3-a]quinozalin-1-one (ODQ) and methylene blue, inhibited the YC-1-induced increase of cyclic GMP level, but did not change significantly the magnitude of the YC-1-induced inhibition of thymidine incorporation and cell number in HUVEC. These results indicate that YC-1-induced cell cycle arrest in HUVEC occurred when the cyclin-CDK system was inhibited just as p21 and p27 protein levels were augmented. This YC-1-induced antiproliferation effect in HUVEC is via a cyclic GMP-independent pathway