MCS-5A, a Novel Sangivamycin Analogue, Induces G1/G2 Phase Arrest and Apoptosis in HL-60 Cells

Chul-Hoon Lee
Department of Medical Genetics Hanyang University, Seoul Korea

The central role of cyclin-dependent kinases (CDKs) in cell cycle regulation makes them a promising target for studying inhibitory molecules that can modify the degree of cell proliferation. The discovery of specific inhibitors of CDKs such as MCS-5A has opened the way to investigation and design of anticancer compounds. A novel , MCS-5A is a potent inhibitor of CDKs. The mechanism of MCS-5A-mediated cell killing is not well defined. We investigated the involvement of cell cycle regulatory events during MCS-5A mediated apoptosis in human pro myeloid HL-60 cells. MCS-5A resulted in apoptosis, inhibition of cell growth, and G1,G2 phase arrest of the cell cycle, in a time-dependent fashion. Treatment of the human promyelotic HL-60 cells with MCS-5A results in inhibition of the phosphorylation of retinoblastoma protein, a critical step for G1/S transition. The kinase activities of G1/S and G2 cyclin-dependent kinases, CDK4 and CDK1, are inhibited in HL-60 cells treated with MCS-5A. Furthermore, MCS-5A has little effect on the expression levels of CDK2, but decreases the levels of CDK4 and CDk1. MCS-5A increases the levels of the cyclin-dependent kinase inhibitors p16 and had little effect on those of p21 and p27. Most interesting is the ability of MCS-5A to induce partner switching for several CDK inhibitors. MCS-5A promotes binding of p16 to CDK4. Furthermore, MCS-5A treatment results in an increased binding of p16 to CDK4. These data suggest that MCS-5A-mediated induction of P16 INK4A results in an imposition of artificial checkpoint at G1.