Proc. KMB Annual Meeting
June 24-26, 2003, Muju, Korea

MCS-C2, a Novel Cyclin-Dependent Kinase Inhibitor, Induces Cell Cycle Arrest and Apoptosis in Human Cancer Cell Lines

C.H. Lee, M. Kim, and Y.H. Cho

Department of Medical Genetics, College of Medicine, Hanyang University, Seoul, Korea

Background and Purpose

In an attempt to search for a specific inhibitor of cell cycle regulation in human cancer cells, we synthesized a novel analogue of toyocamycin, MCS-C2 (Fig. 1). The purpose of this study is to verify the effects of MCS-C2 on the cell cycle progression, and to clarify the action of mechanism on MCS-C2-inducing cell cycle arrest and apoptosis in prostate cancer cells

Materials and Methods

LNCaP (Rb+/+, p53+/+), DU145 (Rb-/-, p53-/-), and PC3 (Rb+/+, p53-/-) treated with MCS-C2 were evaluated for antiproliferative effect and apoptosis using cell viability test, protein kinase assay, Flow cytometric analysis, TUNEL assay (Fig. 2), and microscopic examination. To clarify the action of mechanism of MCS-C2, we also performed immunoblot assay for the regulatory proteins involved in cell cycle progression (Fig. 3) and apoptotic induction.

Results

Treatment of PC3 cell with MCS-C2 resulted in the enhanced expression of E2F1 and rapid degradation of cyclin B in the absence of the modulation of mRNA levels; this was accompanied by the G1 phase arrest of the cell cycle and subsequent apoptosis. The elevated level of E2F1 was due to the enhanced stability of the molecule demonstrating a prolonged half-life. MCS-C2 modulates the expression of E2F1 and cyclinB through the simultaneous stimulation and inhibition of the cyclin B and E2F1 ubiquitination. However, in DU145 cell, MCS-C2 induced up-regulation of cdc2 and cyclin B associated with G2 phase arrest and apoptosis. MCS-C2 inhibited proteasome-dependent degradation of cyclin B, resulting in a sustained activation of cyclinB/cdc2 and a cell cycle arrest in mitosis. Indeed, cdc2 up-regulation occurred in cells arrested in a G2/M phase. LNCaP cells treated with MCS-C2 led to post-translational stabilization of p53, activation of downstream target genes, and induction of cell cycle arrest and apoptosis. Taken together, these results indicated that MCS-C2 induces cell cycle arrest and apoptosis in prostate cancer cells. This effect appears to be mediated via regulation of protein ubiquitiantion pathway.

Conclusion

Our results suggest that MCS-C2 represents a novel antitumor agent distinct from toyocamycin with therapeutic potential against a range of prostate cancer cells.

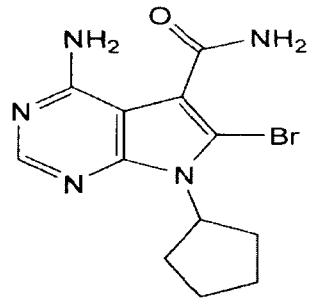

Fig. 1. Chemical structure of MCS-C2.

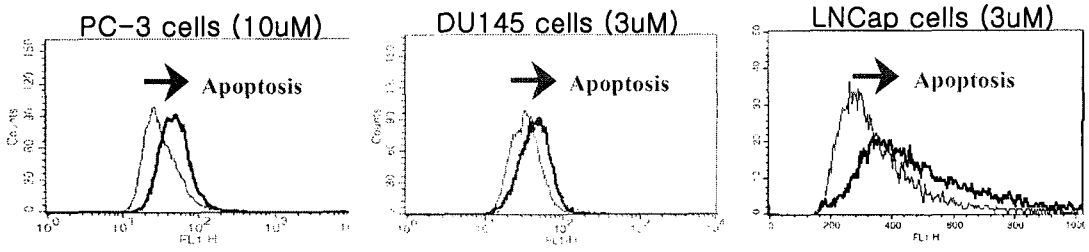

Fig. 2. Effects of MCS-C2 on apoptotic induction in various prostate cancer cells (TUNEL assay).

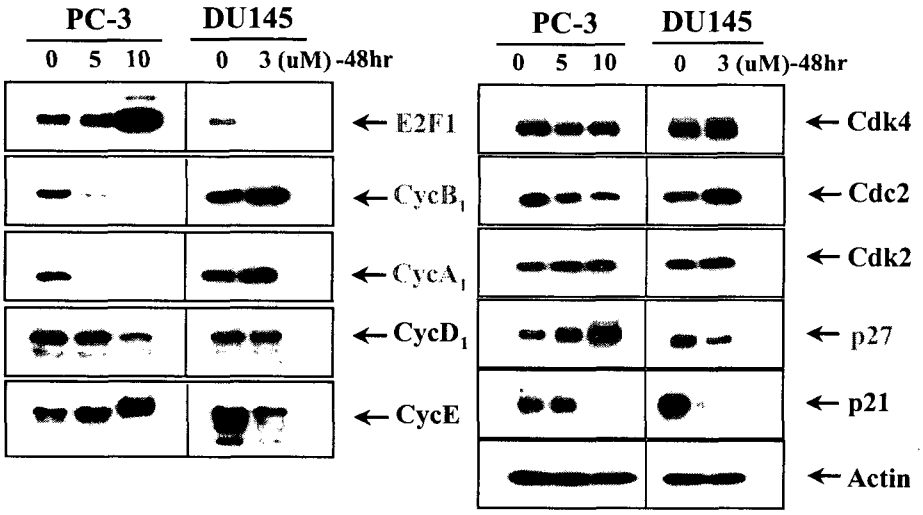

Fig. 3. Effect of MCS-C2 on protein expression of Cdks, cyclins, and CKIs in prostate cancer cells.