

DUAL ACTION OF CYCLIN-DEPENDENT KINASE INHIBITORS: INDUCTION OF CELL CYCLE ARREST AND APOPTOSIS. A COMPARISON OF THE EFFECTS EXERTED BY ROSCOVITINE AND CISPLATIN

Józefa Węsierska-Gądek[#], Marieta Gueorguieva, Marcel Horky*

Cell Cycle Regulation Group, Institute of Cancer Research, University of Vienna, Borschkegasse 8a, A-1090 Vienna, Austria; *Department of Pathological Physiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

Dual action of cyclin-dependent kinase inhibitors: induction of cell cycle arrest and apoptosis. A comparison of the effects exerted by roscovitine and cisplatin. J. WĘSIERSKA-GĄDEK, M. GUEORGUIEVA, M. HORKY. Pol. J. Pharmacol., 2003, 55, 895–902.

Cyclin-dependent kinases (CDKs) have recently raised considerable interest in view of their key role in the regulation of the cell cycle progression. In proliferating cells, distinct CDKs associated with specific cyclins coordinate in an orchestrated way the appropriate transition between different phases of the cell cycle. Mutations and/or aberrant expression of distinct CDKs and their regulatory components lead to uncontrolled proliferation and finally to carcinogenesis. However, in post-mitotic neurons, all CDKs with the exception of CDK5 are silent. CDK5, a proline-directed serine/threonine kinase exhibiting a close structural homology to the mitotic CDKs, binds to p35, the neuron-specific regulatory subunit of CDK5. CDK5 is very abundant in mature neurons and seems to regulate neurotransmitter release through phosphorylation and down-regulation of calcium channel activity. Therefore, the inhibition of CDKs in neurons after oxidative stress and in neurodegenerative disorders has a protective action.

Selective CDKs inhibitors were developed as promising drugs for cancer therapy due to their ability to arrest cell cycle progression. The aim of this study was to compare the anti-proliferative effect of roscovitine (ROSC), a potent CDKs inhibitor, with that of cisplatin (CP) on human breast cancer MCF-7 cells. ROSC exerted stronger inhibitory effect on proliferation and cell cycle progression of MCF-7 than CP. Accumulation of G₂/M arrested cells starting 6 h after onset of ROSC treatment coincided with a strong up-regulation of the p53. Reconstitution with caspase-3 sensitized MCF-7 cells to CP action. It implicates that ROSC inhibits more selectively and efficaciously the proliferation of human breast carcinoma cells.

Key words: *apoptosis, G₂/M arrest, MCF-7 cells, p53 up-regulation, p53 nuclear accumulation, PARP-1 cleavage, caspases-3 reconstitution, FACS analysis*

[#] correspondence; e-mail: Jozefa.Antonia.Gadek-Wesierski@univie.ac.at