PRELIMINARY COMMUNICATION

CELL CYCLE ARREST INDUCED IN HUMAN BREAST CANCER CELLS BY CYCLIN-DEPENDENT KINASE INHIBITORS: A COMPARISON OF THE EFFECTS EXERTED BY ROSCOVITINE AND OLOMOUCINE

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Cyclin-dependent kinases (CDKs) are serine/threonine kinases that play a key role in the regulation of the cell cycle progression. In proliferating cells, distinct CDKs activated upon complexing with specific cyclins and upon site-specific phosphorylation coordinate in an orchestrated way the appropriate transition between consecutive phases of the cell cycle. Aberrant expression or altered activity of distinct CDK complexes results in escape of cells from the cell cycle control and leads to malignant transformation. Therefore, the inhibition of CDKs in malignant cells provides a new strategy in the fight against cancer. Recently, selective CDK inhibitors targeting distinct CDKs were developed. They represent promising anti-cancer drugs due to their strong anti-proliferative efficacy combined with a relative low direct cytotoxicity.

The aim of this study was to compare the effect of two related CDK inhibitors: roscovitine (ROSC) and olomoucine (OLO) on the cell cycle progression in human breast cancer MCF-7 cells. Both examined CDK inhibitors differentially affected the cell cycle progression in MCF-7 cells. Whereas ROSC arrested cells in G2/M, OLO inhibited cells at S to G2 transition and increased the number of cells residing in the S-phase. Moreover, both CDK inhibitors modulated the cell cycle progression with distinct kinetics. Accumulation of G2/M-arrested cells beginning 6 h after exposure of cells to ROSC coincided with a strong up-regulation of the p53. Interestingly, ROSC triggered apoptosis in MCF-7 cells by activation of mitochondrial pathway. Loss of the integrity of mitochondrial membrane observed after exposure of cells to ROSC for 6 h led to release of distinct mitochondrial proteins, e.g. apoptosis inducing factor (AIF). In contrast to ROSC, OLO-induced cell cycle changes could be detected after 12 h of the treatment. OLO did not up-regulate p53 protein. It indicates that both examined CDK inhibitors are selective and block the cell cycle progression of human breast carcinoma cells at different phases.

**Keywords:** G2/M arrest, MCF-7 cells, p53 up-regulation, AIF release, apoptosis, mitochondrial dissipation, PARP-1 cleavage, FACS analysis

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