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THE EFFECTS OF ORNITHINE DECARBOXYLASE ON ANTI-APOPTOSIS AND CELL CYCLE IN CANCER CHEMOTHERAPEUTIC DRUGS, INCLUDING ETOPOSIDE, PACLITAXEL AND CISPLATIN

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BACKGROUND/AIMS: Ornithine decarboxylase (ODC) is a key enzyme for the synthesis of polyamines. In our previous studies, overexpression ODC prevents TNF-α and methotrexate-induced apoptosis by reducing reactive oxygen species (ROS), maintaining mitochondrial membrane potential ($\Delta\psi_m$) and inactivating caspases' activity. We further investigated the apoptotic mechanism of other chemotherapeutic drugs (etoposide, paclitaxel and cisplatin) and the effects of ODC on anti-apoptosis and cell cycle.

METHODS: HL-60 cells were transfected with WT-ODC (overexpression ODC), m-ODC (vector control) and Bcl-2 plasmid. Parent cells, WT-ODC and m-ODC cells were treated by drugs, N-acetylcystein (NAC) and putrescine. Apoptosis were assayed by cell viability, DNA gel-electrophoresis and cell-cycle analysis by flow cytometry. ROS and $\Delta\psi_m$ were detected by flow cytometry, and proteins by immunoblotting.

RESULTS: All the drugs induce caspase-dependent apoptosis, ROS generation and disruption of $\Delta\psi_m$ in HL-60 cells. The effect was counteracted by putrescine and NAC. Overexpression of Bcl-2 could maintain $\Delta\psi_m$ and prevent drug-induced apoptosis. The cells with ODC overexpression had the same effects of putrescine and NAC and kept on cell cycles. Overexpression of ODC prevented the decline of Bcl-2 and caspase activation, and increased the expression of cyclin A, E and Cdk4. Moreover, it catalyzed the phosphorylation of Cdk1 and Cdk2.

CONCLUSIONS: Drugs-induced apoptosis is through ROS-dependent, mitochondria-mediated pathways. Overexpressed ODC cells are resistant to apoptosis and keep on the cell cycles without the interference of G1/S arrest caused by etoposide and G2/M arrest by paclitaxel.

Key words: Ornithine decarboxylase, Chemotherapeutic drugs, Apoptosis