Antiproliferative and apoptotic effects of zinc-citrate compound (CIZAR(R)) on human epithelial ovarian cancer cell line, OVCAR-3.


Source
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Abstract

OBJECTIVE:
Zinc inhibits the growth of several carcinoma cells through induction of cell cycle arrest and apoptosis. The intracellular concentration of zinc and its dynamic changes are critically important in cell biology. We investigated the effects of zinc-citrate compound (CIZAR) on normal human ovarian epithelial cells (NOSE) and human epithelial ovarian cancer cell line, OVCAR-3.

METHODS:
To investigate the potential effect of CIZAR on cell growth and survival, cells were treated with different doses and exposed to different times. Intracellular concentration of zinc was measured by colorimetric assay. Mitochondrial aconitase activity was determined in cell extracts using aconitase assay. The flow cytometric assay, DNA laddering, and morphological analysis were done to investigate cytotoxic effects of CIZAR. Molecular mechanism of cell death was investigated by p53, Bcl-xL, Bcl-2, Bax protein, activity of caspase-3 and -12, and activity of telomerase.

RESULTS:
CIZAR-induced zinc accumulation in OVCAR-3 cells was higher than that in NOSE cells. CIZAR(R) treatment resulted in a time- and dose-dependent decrease in cell
number in OVCAR-3 cells in comparison with NOSE cells. M-aconitase activity was significantly decreased in OVCAR-3 cells within 4 h exposure to CIZAR but relatively constant in NOSE cells. The flow cytometric assay, DNA laddering, and morphological analysis indicated apoptosis in OVCAR-3 cells but not in NOSE cells. CIZAR increased the expression of p21(waf1) which is a part of p53-independent pathway and induced reduction of telomerase activity. CIZAR reduced expression of Bcl-2 and Bcl-xL proteins but induced expression of Bax protein. CIZAR induced apoptosis of OVCAR-3 cells by activation of caspase-12 and caspase-3 pathway.

CONCLUSIONS:

Exposure to CIZAR induces apoptosis in OVCAR-3 cells which accumulate high intracellular levels of zinc, but not in NOSE cells, which do not accumulate high levels of zinc. CIZAR(R) prevents the proliferation of OVCAR-3 cells by inactivation of m-aconitase activity and induces apoptosis by induction of proapoptotic gene (Bax), repression of antiapoptotic genes (Bcl-2, Bcl-xL), and consequently activation of caspase-3. CIZAR also induced activation of caspase-12. The CIZAR will offer new window in prevention and treatment of epithelial ovarian cancer.

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