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Copper Chelation by 3-(Bromoacetyl) Coumarin Derivative Induced Apoptosis in Cancer Cells: Influence of Copper Chelation Strategy in Cancer Treatment

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Abstract : Copper is an essential trace element required for pro-angiogenic co-factors including vascular endothelial growth factor (VEGF). Elevated levels of copper are found in various types of cancer including prostrate, colon, breast, lung and liver for angiogensis and metastasis. Therefore, targeting copper via copper-specific chelators in cancer cells can be developed as effective anticancer treatment strategy. In continuation of our pursuit to design and synthesize copper chelators, herein we opted for a reaction to incorporate di-(2-picolyl) amine in 3-(bromoacetyl) coumarin (parent backbone) for the synthesis of complex 1. We evaluated lipid peroxidation, protein carbonylation, ROS generation, DNA damage and consequent apoptosis by complex 1 in exogenously added Cu(II) in human peripheral lymphocytes (simulate malignancy condition). Results showed that Cu(II)-complex 1 interaction leads to cell proliferation inhibition, apoptosis, ROS generation and DNA damage in human lymphocytes, and these effects were abrogated by cuprous chelator neocuproine and ROS scavengers (thiourea, catalase, SOD). This indicates that complex 1 cytotoxicity is due to redox cycling of copper to generate ROS which leads to pro-oxidant cell death in cancer cells. To further confirm our hypothesis, using the rat model of diethylnitrosamine (DEN) induced hepatocellular carcinoma; we showed that complex 1 mediates DNA breakage and cell death in isolated carcinoma cells. Membrane permeant copper chelator, neocuproine, and ROS scavengers inhibited the complex 1-mediated cellular DNA degradation and apoptosis. In summary, complex 1 anticancer activity is due to its copper chelation capability. These results will provide copper chelation as an effective targeted cancer treatment strategy for selective cytotoxic action against malignant cells without affecting normal cells.

Keywords : cancer treatment, copper chelation, ROS generation, DNA damage, redox cycling, apoptosis
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