Selective anticancer copper(II)-mixed ligand complexes: targeting of both ROS and proteasome

CHEW HEE NG, Siew Ming Kong, Yee Liang Tiong, Mohd Jamil Maah, Nurhazwani Sukram, Munirah Ahmad and Alan Soo-Beng Khoo
Metallomics, 2014, Accepted Manuscript

DOI: 10.1039/C3MT00276D
Received 30 Sep 2013, Accepted 31 Jan 2014
First published online 05 Feb 2014

Abstract:

Copper compounds can be alternatives to platinum-based anticancer drugs. This study investigated the effects of a series of ternary copper(II) complexes, \([\text{Cu(phen)(aa)(H}_2\text{O)}\text{NO}_3.\text{xH}_2\text{O} 1-4 (\text{phen = 1,10-phenanthroline; aa = gly (1), DL-ala (2), sar (3), C-dmg (4))}, \text{on metastatic and cisplatin-resistant MDA-MB-231 breast cancer cells and MCF10A non-cancerous breast cells, and some aspects of the mechanisms. These complexes were distinctively more antiproliferative towards and induced greater apoptotic cell death in MDA-MB-231 than in MCF10A cells. 2 and 4 could induce cell cycle arrest only in cancer cells. Further evidence from DCFH-DA assay showed higher induction of reactive oxygen species (ROS) in treated cancer cells but minimal ROS increase in normal cells. DNA double-strand breaks, via a \(\gamma\)-H2AX assay, were only detected in cancer cells treated with 5 \(\mu\)M of the complexes. These complexes poorly inhibited chymotrypsin-like activity in 20S rabbit proteasome while they did not inhibit the three proteolytic sites of MDA-MB-231 cells at 10 \(\mu\)M. However, the complexes could inhibit degradation of ubiquinated proteins of MDA-MB-231 cells. In addition, compound 4 was found to be effective against cervical (Hela), ovarian (SKOV3), lung (A549, PC9), NPC (Hone1, HK1, C666-1), breast (MCF7, T47D), lymphoma leukemia (Nalmawa, HL60) and colorectal (SW480, SW48, HCT118) cancer cell lines with IC50 values (24 h) in the 1.7 – 19.0 \(\mu\)M range. Single dose NCI60 screening of 4 showed the complex to be highly cytotoxic to most cancer cell types and more effective than cisplatin.

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