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Design and development of novel copper-based drugs for the treatment of human osteosarcoma

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Osteosarcoma (OS) is a frequent bone cancer, affecting largely children and young adults. Cisplatin (CDDP) has been efficacious in the treatment of different cancer such us OS but the development of chemoresistance and important side effects leading to therapeutic failure [1]. Novel therapies including copper compounds have shown to be potentially effective as anticancer drugs and one alternative to usually employed platinum compounds [2].

The goal of this work is the design, development and evaluation of the *in vitro* and *in vivo* antitumoral activity and dilucidate the molecular targets of a diferent Cu(II)-complexes (CuHL1, CuHL2, CuHL3) with tridentate hydrazone derived from tiophen and furan as a ligands against human OS MG-63 cells.

Anticancer activity on MG-63 cell line was evaluated in OS monolayer and spheroids. The three complexes significantly impaired cell viability in both models showing IC_{50} in 2D models around 2 µM and around 9 µM in 3D models ($p < 0.001$). Additional cell studies demonstrated that the Cu-complexes inhibit cell proliferation and conveys cells to apoptosis, determined by flow cytometry. CuHL1 showed a great genotoxicity, evaluated by comet assay. Proteomic analysis by Orbitrap Mass Spectometry identified 27 differentially expressed proteins: 17 proteins were found overexpressed and 10 underexpressed in MG-63 cells after the CuHL treatment. The response to unfolded protein was the most affected biological process. In addition, *in vivo* antitumor effects of the compound were evaluated on human OS tumors xenografted in nude mice. CuHL treatment, at a dose of 2 mg/kg i.p., given three times/week for one month, significantly inhibited the progression of OS xenografts and was associated to a reduction in mitotic index and to an increment of tumor necrosis ($p < 0.01$). Administration of standard-of-care cytotoxic agent CDDP, following the same treatment schedule as CuHL, failed to impair OS growth and progression.

Taking into account the anticancer activity of CuHL and the scarce options on the treatment of OS, our results indicate that this complex is an engaging candidate for potential antitumor therapies and it would be attractive to further test CuHL1 in in vivo orthotopics OS models.

References

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