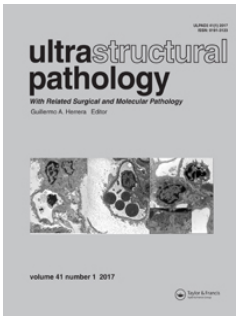

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Ultrastructural features of cells following incubation with metal complexes using phenanthroline-based ligands: The influence of the metal center

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intercellular collagen fibers, seem to support the WD bacteria colonization.

(3) Macrophages with overloaded phagosomes with lamellae have limited digestion capacity and single phagocytosed bacteria may represent the reason of the prolonged persistent of infection.

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Ultrastructural features of cells following incubation with metal complexes using phenanthroline-based ligands: The influence of the metal center

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Polypyridyl metal-based complexes are known to present high structural versatility due to the different metal coordination modes and the wide range of ligands commercially and synthetically available. Such versatility can be explored to obtain a variety of structures and physicochemical properties which can be tuned to improve the usefulness of this class of compounds for catalysis, molecular electronic devices, fluorescent probes, and more recently as enzyme inhibitors and cytotoxic agents. Metal complexes using phenanthroline-based ligands are reported to be active against various pathologic conditions including cancer, microbial, and fungal infections [1].

Within this scope a series of transition metal complexes with the general formula [M(SalGly)(Phen)] (M = Cu, Zn, V) (phen = phenanthroline) (SalGly = salycylaldehyde-glycine Schiff base) were prepared. The complexes were synthetized and characterized by the usual analytical techniques [2,3]. The cytotoxic activity of the complexes was assessed against human tumor cells (A2780, ovarian) by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) analysis was carried out in cellular fractions to evaluate the distribution of the complexes inside the cells. Electronic microscopy (TEM) was used to evaluate the effects at cellular organelle level, using thin section TEM described before [4].

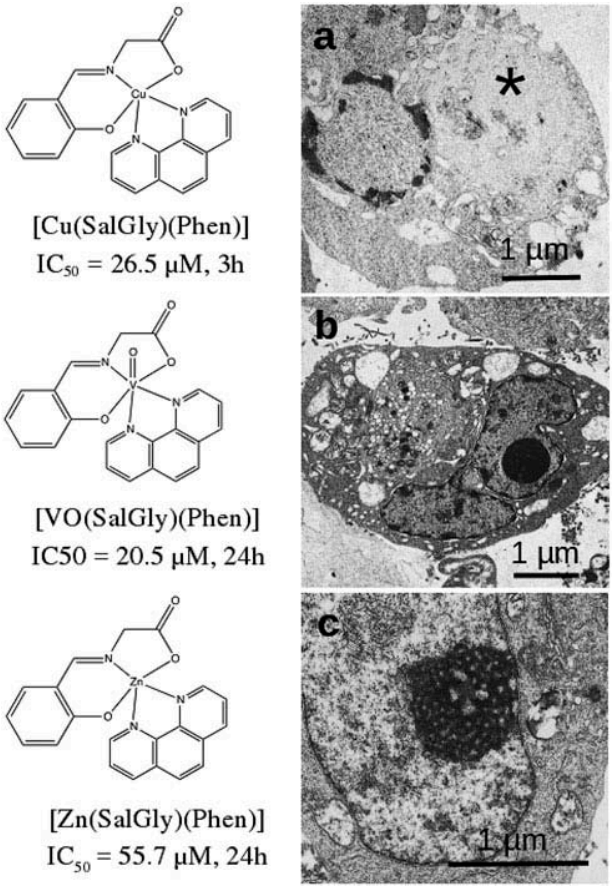

Figure 1. Left column [M(SalGly)(phen)] (M = Cu, Zn, V) molecular structures; Right column: Electron microscope effects of the A2780 cells treated with the corresponding complexes (*). (a) Copper complex – marked disruption of the cellular architecture and nuclear chromatin condensation. A large accumulation of microfilaments can consistently be observed in the cytoplasm (M); (b) Vanadium complex – vesiculation and disruption of the endomembrane system and marked alterations of the nuclear profile; (c) Zinc complex – mitochondrial damage.

The complexes present moderate cytotoxic activity against the ovarian cells with exception of the Cu congener which display the same activity at shorter incubation times. The complexes are retained particularly in the membrane fraction for the V complex and differ for the Zn complex which is mainly retained in the cytosol fraction. Noteworthy is that the uptake in terms of metal content is much higher for Cu and Zn complexes. The Cu complex is the only one that followed an uptake versus cytotoxic activity relationship. The uptake profile and activity studies of a Sm congener are under way.

Electron microscopy studies confirm the higher cytotoxic activity of the Cu complex, the marked membrane alterations in the membrane – associated with V complex, and the least alterations in the Zn complex treated cells that show mitochondrial degenerative changes (Fig 1).

Funding

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Unraveling the mode of action of new promising polymer–ruthenium conjugates

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One of the major challenges in cancer chemotherapy comprises selective drug delivery to cancer cells. Currently, only few drugs possess such inherent selectivity, making the development of a more general and effective cancer-targeted drug delivery mandatory. In this framework, polymer–drug conjugates constitute a promising alternative to conventional drug delivery in cancer therapy. Macromolecules selectively accumulate in malignant tissues compared to healthy tissues by either passive or active targeting, precluding the undesirable side effects generated by free low molecular weight drugs. Importantly, macromolecules internalize into cells by endocytosis [1], being this process recognized to overcome the multi-drug resistance phenomenon that renders tumors resistant to chemotherapy, and confers poor prognosis for patient survival.

During the last years, our research group has been developing a robust ruthenium family of compounds as potential anticancer agents, with the pioneer role of the "Ru(II)Cp" (Cp = cyclopentadienyl) derived complexes [2]. Factors that modulate the cytotoxic activity of Ru-based drugs are numerous and seem to be dependent on the family of compounds under scrutiny. However, a general tendency has been observed: all the studied low molecular weight Ru(II)Cp-derived complexes exert their cytotoxic action through the cell membranes [3], while compounds bearing the same cytotoxic fragment, but having polymeric ligands (polymer–ruthenium conjugates, RuPMC) are