Therapeutic Potential of Metal Complexes with Isatin Derivatives

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In the last years, many metal complexes were developed as efficient drugs for many diseases including cancer, diabetes, and inflammation, although only a few ones have been already approved by FDA. These complexes can act as binders to DNA, and when redox-active they can cause oxidative damage through the formation of reactive oxygen species (ROS), or otherwise can catalyze hydrolytic reactions. In our lab, we have been investigating the influence of different imine ligands in the reactivity of essential metal ions, mainly copper or zinc, at the aim of developing alternative metallodrugs to cisplatin and derivatives, the most studied and used compounds as antitumor agent.

Our ligands were designed based in oxindole derivatives described in the literature and that have previously entered in anticancer clinical tests (phase II or III) as promising pharmacological compounds [1]. They usually are derivatives of 2,3-dioxindoline (isatin), a metabolite of amino acids encountered in human fluids. Copper ion can play different functions in many proteins (oxidases, reductases, antioxidant enzymes, etc.), where its reactivity is remarkably modified by the coordinating environment, and its homeostasis is tightly controlled. On the other hand, analogous zinc complexes serve as a non-redox active counterpart.

In our investigations, we verified that these oxindolimine-metal complexes are thermodynamically very stable, and are able to enter the cells, binding efficiently to DNA structure at major or minor groves, and causing oxidative damage, mainly at purine or pyrimidine bases [2]. Further, they inhibit proteins involved in DNA topology, as topoisomerase IB [3], and cyclin-dependent kinases that control the cellular cycle, as CDK1 or CDK2 [4]. Therefore, they can trigger apoptosis, being much more toxic to tumor cells (HeLa, neuroblastomas, sarcomas, or melanomas) than to non-cancer cells (fibroblastos P4).

All these processes indicated that these metal complexes act as multifunctional compounds by different mechanisms, modulated by the metal as well as by the ligands. Theoretical simulations (DFT, molecular dynamics) corroborated these data, giving support to our experimental results. In the case of similar homobinuclear species (CuLCu), mimetics of tyrosinase, melanoma cells are particularly sensitive to them, especially in the presence of high level of melanogenesis [5]. More recently, heterobinuclear compounds (CuLPt) showed a synergistic effect of both metal centers, bound to the same imine ligand. Platinum center leads to stronger bind to DNA, while copper center is predominantly responsible for further mitochondrial damage, and inhibition of proteins.

References:

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