N-based ligands with intracellular oxidative activity as potential anti-tumor agents

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Tumor cells have persistently higher levels of Reactive Oxygen Species (ROS) than normal cells which is a consequence of their abnormal metabolism together with genetic alterations [1,2]. The constitutive oxidative stress of cancer cells provides a specific target for the design of novel redox-based anticancer therapies, as cancer cells are very vulnerable to pro-oxidant agents such as transition metal based-complexes [3]. When accumulated inside the cells, metals such as iron, manganese or copper, undergo cycling redox reactions that generate high levels of ROS, generating additional ROS, which are likely to increase the oxidative stress above the cytotoxic threshold, leading to a cell death [4]. Therefore, we evaluated the antitumoral properties of five polyamine Fe-Complexes and their corresponding uncomplexed ligands. Only the ligands displayed antiproliferative activity against breast adenocarcinoma MCF-7 and pancreas adenocarcinoma CAPAN-1 cancer cell lines. The most active compounds were selected to further analyzed their cytotoxicity against a broad panel of tumor and non-malignant cell lines and their ability to inhibit the clonogenicity of cancer cells. In addition, the ability of the compounds to generate ROS inside the cells and the influence of the intracellular iron in their cytotoxicity was evaluated. Our results reveal that three ligands display an interesting anticancer activity, with higher IC_{50} values in non-malignant cells than in tumor cells and exhibit inhibitory effect on the clonogenicity of tumor cells. Moreover, the ligands are not hemolytic against human red blood cells. We determine that the ligands are inducers of oxidative stress and that ROS induction is associated to their strong capactity to bind intracellular iron and generate the highly oxidant iron coordination complexes inside the cells, inducing the cell death. These results indicate that these ligands may be a potential prooxidant anticancer agents. [1] Cairns RA et al. Nat Rev Cancer 2011. [2] Luo J et al. Cell 2009. [3] Montero AJ et al. Drugs 2011. [4] Dixon S et al. Natu. Chem. Bio 2014.