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Insights into the Redox Activity of Platinum(II) Complexes Bearing a Mitochondriotropic Ligand in Cisplatin-resistant Ovarian Cancer Cell Lines

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Cisplatin is a platinum-based drug used for the treatment of many cancer types. Its principal mechanism of action is centered on the irreversible DNA binding forming covalent adducts. In addition, it was also found able to inhibit the redox enzyme Thioredoxin Reductase (TrxR). This selenoenzyme is a key antioxidant protein involved in the redox homeostasis of the cell and it is particularly important in cancer cells where an increased production of reactive oxygen species (ROS) is often observed. Notwithstanding its usefulness in clinic, cisplatin suffers of dose-related side effects and most worryingly of intrinsic or acquired resistance. In order to identify more effective and safe molecules, different cisplatin derivatives have been synthesized throughout the years. Here, we report the effect of a series of novel differentially functionalized platinum(II) complexes endowed with a triphenylphosphine ligand on the viability and redox homeostasis of ovarian cancer cells both sensitive (A2780) and resistant (A2780cis) to cisplatin. First, the antiproliferative effect of the new compounds was assessed on a panel of human cancer cell lines. Interestingly, they were effective in decreasing cell proliferation in all the lines analyzed, overcoming the mechanisms of cisplatin resistance and accumulating quickly in the cells. Investigating on the mechanism of action, we found that the platinum complexes were less effective in DNA platination when compared to cisplatin, while they showed a sub-micromolar inhibitory activity on TrxR. Furthermore, the complexes show a mitochondriotropic behaviour as they are able to induce mitochondrial depolarization. Finally, we found that the new metal-complexes trigger ROS production and induce an imbalance of the redox homeostasis with impact on glutathione levels eventually leading to the initiation of cell death. Thus, these complexes seem promising as they combine the DNA-alkylating action to a potent inhibitory activity on TrxR resulting effective in both cisplatin sensitive and resistant cancer cells.