

Assessing the role of membrane lipids in the action of ruthenium(III) anticancer compounds

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Streszczenie

This work addresses the possible role of the cell membrane in the molecular mechanism of action of two *salan*-type ruthenium complexes that were previously shown to be active against human tumor cells, namely [Ru(III)(**L1**)(PPh₃)Cl] and [Ru(III)(**L2**)(PPh₃)Cl] (where **L1** is 6,6'-(1*R*,2*R*)-cyclohexane-1,2-diylbis(azanediyl)bis(methylene)bis(3-methoxyphenol); and **L2** is 2,2'-(1*R*,2*R*)-cyclohexane-1,2-diylbis(azanediyl)bis(methylene)bis(4-methoxyphenol)). One-component membrane models were first used, a disordered fluid bilayer of dioleoylphosphatidylcholine (DOPC), and an ordered rigid gel bilayer of dipalmitoylphosphatidylcholine. In addition, two quaternary mixtures of phosphatidylcholine, phosphatidylethanolamine, sphingomyelin and cholesterol were used to mimic the lipid composition either of mammalian plasma membrane (1:1:1:1 mol ratio) or of a cancer cell line membrane (36.2:23.6:6.8:33.4 mol ratio). The results show that both *salan* ligands **L1** and **L2** bind relatively strongly to DOPC bilayers, but without significantly affecting their structure. The ruthenium complexes have moderate affinity for DOPC. However, their impact on the membranes was notable, leading to a significant increase in the permeability of the lipid vesicles. None of the compounds compromised liposome integrity, as revealed by dynamic light scattering. Fluorescence spectroscopy studies revealed changes in the biophysical properties of all membrane models analyzed in the presence of the two complexes, which promoted an increased fluidity and water penetration into the lipid bilayer in the one-component systems. In the quaternary mixtures, one of the complexes had an analogous effect (increasing water penetration), whereas the other complex reorganized the liquid ordered and liquid disordered domains. Thus, small structural differences in the metal ligands may lead to different outcomes. To better understand the effect of these complexes in cancer cells, the

membrane dipole potential was also measured. For both Ru complexes, an increase in the dipole potential was observed for the cancer cell membrane model, while no alteration was detected on the non-cancer plasma membrane model. Our results show that the action of the Ru(III) complexes tested involves changes in the biophysical properties of the plasma membrane, and that it also depends on membrane lipid composition, which is frequently altered in cancer cells when compared to their normal counterparts.

Słowa kluczowe

biomimetic lipid membrane, ruthenium complexes, membrane leakage, lipid domains, fluorescence spectroscopy, membrane dipole potential

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