Abstract

Ferrocenes as Potential Anticancer Drugs: Determination of the Mechanism of Action †

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Abstract: Chemotherapy is an essential treatment that still plays a vital role in cancer treatment worldwide. The ferrocene derivatives of the general formula [Fe{(η⁵-C₅H₄CH₂(p-C₆H₄)CH₂(N-het))₂}] bearing modified six and five membered N-heterocycles were tested in vitro for their cytotoxic properties against ovarian cancer cell lines A2780 and SK-OV-3. These ferrocene complexes displayed cytotoxicity in low micromolar concentrations against both cell lines. To study cellular uptake of particular ferrocenes into tumor cells, we used differential pulse voltammetry and ICP-MS. We confirmed the crucial role of transferrin receptors in the process of intracellular accumulation of these ferrocenes. Interestingly, the rate of intracellular accumulation of particular ferrocenes clearly mirrored the cytotoxicity of these organometallic compounds. Deeper investigation of the mechanism by which ferrocenes kill tumor cells revealed induction of apoptosis associated with significant increase of reactive oxygen species. In conclusion, our screening identified several ferrocene derivatives exerting promising cytostatic activity in vitro. Further investigation led to the identification of the mechanism of action of these potential anticancer agents, which represents an important milestone in preclinical anticancer drug discovery programs. This work was supported by the project MEYS-NPS I-LO1413, MH CZ-DRO (MMCI, 00209805) and Czech Science Foundation project 17-05838S.

Keywords: ferrocene; ovarian cancer; cellular uptake; transferrin; reactive oxygen species

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