Palladium (II)-based novel approach to kill cancer stem cells of breast cancer

E. Ulukaya1, S. Aydinlik2, M. Erkis3, F. Ay3, V.T. Yilmaz3
1Clinical Biochemistry, Uludag University Medical Faculty, Bursa, Turkey
2Biology, Science and Arts Faculty of Uludag University, Bursa, Turkey
3Chemistry, Science and Arts Faculty of Uludag University, Bursa, Turkey

Aim/Background: The outcome of breast cancer patients is still far from a success. Therefore, novel chemotherapeutics are still needed. However, new drugs are expected to kill not only cancer cells but also cancer stem cell (CSC) population that is a small subgroup in a tumor tissue and responsible for the treatment failure and relapses. So, it is of great importance to kill these therapy-resistant cells. Our research team recently synthesized a palladium (Pd) (II)-based compound that is formulated as \( \text{Pd(sac)(terpy)(sac)} \cdot 4\text{H}_2\text{O} \). We previously published its cytotoxic potential on human breast cancer cells in vitro and in vivo (Ulukaya, EJMC, 2011). In the present study, its cytotoxic potential against the cancer stem cells was investigated.

Methods: Breast cancer stem cells (CD44+/CD24−/low cells) were propagated from MCF-7 cell line (parental) and then mammosphere formation was induced to enrich the population of cancer stem cells. The cytotoxic activity of Pd (II) complex on MCF-7 cell line and MCF-7-derived spheres (mammospheres, MCF-7s) was investigated via the ATP viability assay. Caspase-cleaved cytokeratin 18 (M30), which is a well-known marker for apoptosis and total cytokeratin 18 (M65) were used to determine the mode of cell death (apoptosis/necrosis). The results were further confirmed with Hoechst 43332/PI fluorescence staining for nuclear morphology and cell membrane intactness.

Results: The Pd (II) complex (1.56 - 100 µM) resulted in the growth inhibition in a dose and time dependent manner in both types of cells. However, the mammospheres (CSCs, MCF-7s) were only affected at relatively higher doses (25 and 50 µM), suggesting their relative resistance against the compound in relative to the parental cells (MCF-7 cells). Both types of cells underwent apoptosis that is judged by the increments of M30 levels and the presence of pyknotic nuclei. However, the relative resistance still persisted in cancer stem cells (MCF-7s), requiring the higher doses than those used for MCF-7 cells.

Conclusions: Cancer stem cell-killing activity of this Pd (II)-based compound deserves further attention to proceed into animal and/or clinical studies. This study is supported by TUBITAK (The Scientific and Technological Research Council of Turkey) with a project number of 114Z269.

Disclosure: All authors have declared no conflicts of interest.