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Abstract

Palladium-Spermine Complex (Pd_2Spm) Triggers Autophagy and Caspase-Independent Cell Death in Triple-Negative Breast Cancer Cells †

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Abstract: Triple-negative breast cancer (TNBC) is an aggressive breast carcinoma with a poor prognosis. Current treatment options with platinum-(Pt)-based chemotherapeutics are limited by toxicity/acquired resistance, which has prompted the search for novel metal-based compounds. Dinuclear palladium(II)-spermine chelate (Pd_2Spm) has previously shown promising pharmacokinetics and in vivo antitumor effects. However, its impact on chemotherapy-resistant TNBC is still to be addressed. This work developed a cell model of cisplatin resistance and compared the anticancer/antiproliferative effects of cisplatin (reference Pt-based drug) and Pd_2Spm in TNBC cells sensitive (MDA-MB-231) and resistant to cisplatin (MDA-MB-231/R). Pd_2Spm displayed a similar antiproliferative potency in MDA-MB-231 and MDA-MB-231/R cells, while cisplatin showed ca. 18-fold lower potency towards MDA-MB-231/R cells. When focusing on cell death, the incubation of Pd_2Spm with either necrostatin-1 (necroptosis inhibitor), Z-VAD (apoptosis inhibitor), or 3-methyladenine (3-MA, autophagy inhibitor) showed that 3-MA could rescue Pd_2Spm-induced growth inhibition in MDA-MB-231 and MDA-MB-231/R cells. Furthermore, in MDA-MB-231 cells, Pd_2Spm triggered higher LC3-II levels and more profound Beclin-1 inhibition than cisplatin. Regarding apoptosis, Pd_2Spm did not induce the cleavage of caspase-3, and the co-incubation of both Pd_2Spm and Z-VAD yielded only marginal effects in preventing phosphatidylserine externalization compared to cisplatin. Thus, the present data provide more evidence on Pd_2Spm's cell death mechanisms, which trigger a caspase-independent cell death with autophagy involvement. In addition, the potential of Pd_2Spm to overcome chemotherapy resistance is promising.

Keywords: breast cancer; TNBC; cisplatin; Pd2Spm; Pd(II)-based drugs

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