J Stem Cell Res Ther 2017, 7:9 (Suppl)
DOI: 10.4172/2157-7633-C1-030

Investigation into the differences in anoikis responses of tumorigenic and non-tumorigenic breast cell lines after exposure to a novel 2-methoxyestradiol derivative

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Breast cancer has become the most commonly diagnosed cancer in many sub-Saharan African countries. In South Africa, it has been observed that there are varied lifetime risks for developing breast cancer based on ethnicity. For instance, while white females have a much higher chance to be diagnosed, black African females with triple negative breast cancer (TNBC) have a much poorer prognosis. In the search for new and improved therapies to target especially triple negative breast tumors we have designed and synthesized a number of 2-methoxy estradiol (2ME) derivatives. 2ME has been shown to have anti-tumor and anti-angiogenic properties but clinical trials have failed due to low bioavailability of the compound. The aim of this study is to characterize the mode of action of an estrone derivative of 2ME called EE-15-one that has been found to induce rapid cell rounding and detachment of different breast cancer cell lines leading to eventual cell death. Initially, the effect of EE-15-one on different cell lines was assessed using cell count assays after exposure with EE-15-one. These illustrated that there was a loss of cells after short exposure of EE-15-one at low micromolar concentrations in all cell lines. Interestingly, the non-tumorigenic cell line MCF10A was less sensitive to the compound than the TNBC line MDA-MB-231. In contrast, cell rounding was more rapid in MCF10A cells but cells remained attached while MDA-MB-231 cells rounded and detached from the surface. Concurrently, a rapid rise in caspase 8 activity was observed in MCF10A cells after exposure while in tumorigenic cells caspase 8 activity was hardly increased. In contrast, ERK phosphorylation was rapidly increased in MCF10A but not in MDA-MB-231 cells. LDH activity assays reveal that cells enter late apoptosis and cell death only 48 hours after having been exposed to EE-15-one suggesting that EE-15-one does not actively kill the cells but rather induces anoikis. EE-15-one is an estrone derivative of 2ME and is the only non-sulphamoyated derivative we designed that has shown activity against different cancer cell lines. Unlike the other derivatives, EE-15-one seems to induce cell rounding and detachment rather than a block in the cell cycle. Our studies show that the non-tumorigenic cell line initially is more resistant to EE-15-one than the TNBC line MDA-MB-231. This resistance may be due to stronger adhesion by the MCF-10A cells to the substrate compared to MDA-MB-231. Caspase 8 activity is massively induced in MCF10A cells when compared to MDA-MB-231 cells as expected since TNBC cells are more resistant to anoikis. However, the pro-survival signal of ERK phosphorylation is more active in MCF10A than MDA-MB-231 suggesting cell line specific alterations in this signaling pathway. In conclusion, EE-15-one is an estrone derivative of 2ME that induces anoikis in cancer cells and can be used as a tool to better understand anoikis resistance in cancer.

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