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Differential antiproliferative properties of 17β-estradiol analog in combination with dichloroacetic acid on human breast cancer MCF-7 and non-tumorigenic MCF-12A cells

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The differential antiproliferative property of a novel in silico-designed antimitotic 17β-estradiol derivative (C9) in combination with dichloroacetic acid (DCA) was investigated. C9 was modified at positions C2, C3 and C17 from its mother molecule 2-methoxyestradiol. Recent research data has suggested that the modified molecule C9 has a higher binding affinity for carbonic anhydrase II which promotes higher bioavailability. DCA inhibits the mitochondrial gate keeping enzyme pyruvate dehydrogenase kinase (PDK) in cancer cells, thus reactivate mitochondrial respiration. Previously, we have demonstrated that 7.5mM of DCA in combination of 130nM of C9 (24 h) inhibited MCF-7 cell growth by 50.8% when compared to inhibition of MCF-12A cell growth of only 29.3% ($P < 0.05$). Qualitative morphological studies revealed decreased cell density in both types of treated cells, as well as hallmarks of apoptosis and autophagic processes including cell shrinkage, formation of apoptotic bodies, increased lysosomal staining (triple fluorescent staining), DNA fragmentation (confocal microscopy) and vacuolar structure formation (transmission electron microscopy). Cell cycle and annexin V-FITC analysis revealed an increase in the sub-G1 phase in C9+DCA-treated MCF-7 cells which served as an indication of cytotoxicity and selectively target the cancer cells. LC3-II antibody, which binds to component of autophagosome membranes, was quantified and increased 23.2% ($P < 0.05$) in MCF-7 cells after exposure to C9+DCA for 24 h. Tumorigenic MCF-7 cells mitochondrial membrane potential (MMP) depolarization after 24 h treatment with combination therapy was confirmed. Global gene expression analysis (Agilent 44K 60-mer) was performed on both cell lines and the results unveiled structural integrity related genes such as actin gamma 1 (ACTG1) and tubulin alpha 6 (TUBA6) were down regulated. A statistically significant increase of MMP depolarization was observed when JNK inhibitor was added in conjunction with the compounds on both cell lines. However, p38 inhibitor did not cause more MMP depolarization. Interestingly, morphological observation showed addition of p38 inhibitor caused more cell damage than that of the JNK inhibitor. This observation is supported by Cell Index data obtained from xCELLigence. These result demonstrate that both JNK and p38 pathways play a very important pro-proliferative role in both cell lines.

In conclusion, the novel 17β-estradiol derivative C9 in combination with DCA is a potent antiproliferative treatment with properties of selectivity towards tumorigenic cells and warrants further studies as a potential combination chemotherapeutic agent in other cancer cell lines.

Biography

Xiao Xing Stander is a Ph.D student in the field of Cellular and Molecular Physiology at University of Pretoria, South Africa. She is the first female student at the Faculty of Health Science University of Pretoria to upgrade the MSc project into a Ph.D based on her strong academic record and level of research competence. As an emerging young scientist, she has published one paper and two conference proceedings after working on her project shortly after one year. She has also been invited to review papers for popular journals such as Plos One.

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