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Cellular Mechanisms Involved in the Radiosensitization of Breast- and Lung Cancer Cells by Agents Targeting Microtubule Dynamics

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Abstract : Treatment regimens for breast- and lung cancers may include both radiation- and chemotherapy. Ideally, a pharmaceutical agent which selectively sensitizes cancer cells to gamma (γ)-radiation would allow administration of lower doses of each modality, yielding synergistic anti-cancer benefits and lower metastasis occurrence, in addition to decreasing the side-effect profiles. A range of 2-methoxyestradiol (2-ME) analogues, namely 2-ethyl-3-O-sulphamoyl-estra-1,3,5 (10) 15-tetraene-3-ol-17one (ESE-15-one), 2-ethyl-3-O-sulphamoyl-estra-1,3,5(10),15-tetraen-17-ol (ESE-15-ol) and 2-ethyl-3-O-sulphamoyl-estra-1,3,5(10)16-tetraene (ESE-16) were in silico-designed by our laboratory, with the aim of improving the parent compound's bioavailability in vivo. The main effect of these compounds is the disruption of microtubule dynamics with a resultant mitotic accumulation and induction of programmed cell death in various cancer cell lines. This in vitro study aimed to determine the cellular responses involved in the radiation sensitization effects of these analogues at low doses in breast- and lung cancer cell lines. The oestrogen receptor positive MCF-7-, oestrogen receptor negative MDA-MB-231- and triple negative BT-20 breast cancer cell lines as well as the A549 lung cancer cell line were used. The minimal compound- and radiation doses able to induce apoptosis were determined using annexin-V and cell cycle progression markers. These doses (cell line dependent) were used to pre-sensitize the cancer cells 24 hours prior to 6 gray (Gy) radiation. Experiments were conducted on samples exposed to the individual- as well as the combination treatment conditions in order to determine whether the combination treatment yielded an additive cell death response. Morphological studies included light-, fluorescence- and transmission electron microscopy. Apoptosis induction was determined by flow cytometry employing annexin V, cell cycle analysis, B-cell lymphoma 2 (Bcl-2) signalling, as well as reactive oxygen species (ROS) production. Clonogenic studies were performed by allowing colony formation for 10 days post radiation. Deoxyribonucleic acid (DNA) damage was quantified via γ-H2AX foci and micronuclei quantification. Amplification of the p53 signalling pathway was determined by western blot. Results indicated that exposing breast- and lung cancer cells to nanomolar concentrations of these analogues 24 hours prior to γ-radiation induced more cell death than the compound- and radiation treatments alone. Hypercondensed chromatin, decreased cell density, a damaged cytoskeleton and an increase in apoptotic body formation were observed in cells exposed to the combination treatment condition. An increased number of cells present in the sub-G1 phase as well as increased annexin-V staining, elevation of ROS formation and decreased Bcl-2 signalling confirmed the additive effect of the combination treatment. In addition, colony formation decreased significantly. p53 signalling pathways were significantly amplified in cells exposed to the analogues 24 hours prior to radiation, as was the amount of DNA damage. In conclusion, our results indicated that pre-treatment of breast- and lung cancer cells with low doses of 2-ME analogues sensitized breast- and lung cancer cells to γ-radiation and induced apoptosis more so than the individual treatments alone. Future studies will focus on the effect of the combination treatment on non-malignant cellular counterparts.

Keywords : cancer, microtubule dynamics, radiation therapy, radiosensitization
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