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MECHANISM-BASED COMBINATION THERAPY IN CANCER: STUDIES ON CANCER CELLS

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Telomeres play a critical and opposing role in the process of carcinogenesis, serving as an obstacle e during early stages of cell transformation and later a cancer hallmark for unlimited cell proliferation. . Reactivation of telomerase is essential for telomere maintenance in human cancer cells ensuring indefinite proliferation. Targeting telomere homeostasis has become one of the promising strategies in the therapeutic management of tumours. We have recently shown that inhibition of DNA repair factors and telomerase renders cells more sensitive to DNA damaging agents. In addition to inducing telomere dysfunction, inhibition of telomerase decreased tumour cell viability, induced cell cycle arrest and DNA damage. The observed therapeutic potential in the cancer cells improved when they were combined with the inhibition of certain selective DNA repair factors such as poly(ADP-ribose) polymerase-1, DNA-depndent protein kinase (DNA-PKcs), Ataxia Telangiectasia Mutated (ATM) and/or radiation. Interestingly, telomerase inhibitors impede the cell survival and proliferative ability to a greater extent in telomerase-positive cells as compared to alternative lengthening of telomeres-positive cells both in acute and chronic treatments. In addition, our in vitro studies suggest that inhibition of DNA repair pathways and that of telomerase could sensitise cancer cells to radiation and enhance anti-tumour effects. Taken together, our in vitro studies in cancer cells demonstrate that inhibition of DNA repair pathways and that of telomerase could be an alternative strategy to enhance anti-tumour effects and circumvent the possibility of drug resistance.

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