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INCREASING TELOMERASE IN HUMAN CANCER STEM CELLS BY NOVEL COMPOUNDS ENHANCED THE SENSITIVITY OF THE CELLS TO CERTAIN ANTI-CANCER AGENTS

E Priel, T Golochovsky, J Gopas and **M Elkabetz**
Ben-Gurion University of the Negev, Israel

Telomerase, a ribonucleoprotein is responsible for the re-elongation of telomeres and is not or is slightly expressed in somatic cells but it is highly expressed in most of the tumor cells. Telomerase expression is regulated by various factors and recently it was suggested that some mRNA splice variants for human telomerase catalytic subunit (hTERT) regulate the activity of telomerase. The expression of telomerase in cancer stem cells was previously reported but the regulation of its expression and activity in cancer stem cells was not thoroughly investigated. Here we show that the hTERT dominant negative splice variant beta is highly expressed in both the adherent and the mammospheres (cancer stem cells) of human breast cancer cell line (MCF7). We found that telomerase activity in cancer stem cells is also regulated by the relative expressions of the full length and the betta splice variants of TERT. We synthesized novel compounds (AGS) that activate telomerase expression in various human and animal cells as well as, *in vivo*, in animal models. Treating cancer stem cells with these compounds increased the expression of the full length TERT relatively to the beta splice variant. Pretreatment of cancer stem cells with the telomerase increasing compound increase the sensitivity of these cells to anti- cancer agents in general and specifically to topoisomerase inhibitors. The results of this study suggest a novel approach, based on telomerase activation, for increasing the sensitivity of cancer stem cells to chemotherapeutic agents.

priel@bgu.ac.il