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Tumor treating fields (TTFields) induced cancer cell death may be immunogenic resulting in enhanced antitumor efficacy when combined with immune-modulating therapy

Moshe Giladi
Novocure Ltd., Israel

Tumor treating fields (TTFields) are an effective anti-neoplastic treatment modality delivered via non-invasive application of low intensity, intermediate frequency, alternating electric fields. This therapy is approved for the treatment of patients with glioblastoma. Previous investigations have shown that TTFields disrupt microtubules and septin filaments, both of which govern key roles in mitosis. Some of the outcomes of mitosis under TTFields application include abnormal chromosome segregation and ER stress which trigger different forms of cell death. The goal of this study was to evaluate whether TTFields induced cancer cell death can be perceived as immunogenic by the immune system and to explore the possibility of combining TTFields with immune-modulating drugs. Murine Lewis lung carcinoma (LLC) and ovarian surface epithelial (MOSE) cells were treated with TTFields using the inovitro system. The exposure of calreticulin (CRT) on the surface of treated cells was evaluated using flow cytometry. High-mobility group box 1 protein (HMGB1) secretion was measured using ELISA assay. For *in vivo* experiments, immunocompetent C57BL/6 mice were orthotopically implanted with LLC cells and treated with TTFields, anti-PD-1 or combination of the two modalities. Changes in tumor volume were monitored and flow cytometry analysis was performed for phenotypic characterization of tumor infiltrating immune cells. We demonstrate that application of TTFields leads to the exposure of CRT on the cell surface and also promotes release of HMGB1 from cancer cells *in vitro*. *In vivo*, the combined treatment of TTFields and anti-PD-1 led to a significant decrease in tumor volume compared to control group and to animals treated with anti-PD-1 alone. An increase in CD45+ tumor infiltrating cells was observed in both anti-PD-1 and TTFields+anti-PD-1 groups although statistical significance was reached only in the combination treatment group. Interestingly, CD45+ cells from the combination treatment group also demonstrated a significant upregulation of PD-L1 expression on the cell surface. Specifically, this upregulation in the PD-L1 expression was observed in both F4/80+CD11+ cells (macrophages) and CD11c+ cells (dendritic cells) whereas no significant effect on the infiltration pattern of these immune cell populations was noted. Taken together, our results demonstrate that TTFields application potentiates immunogenic cell death in cancer cells and that combining TTFields with specific immunotherapies such as anti-PD-1 might achieve tumor control by further enhancing antitumor immunity.

Biography

Moshe Giladi has joined Novocure in 2005 and served as the Head of the NovoBiotic project until 2008. He was then promoted to Head of Novocure's Preclinical Research leading a team of experts of various fields: Cancer, immunology, cell biology and also responsible for research collaboration with academic institutes. He leads research activities studying tumor treating fields mechanism of action. He has received his PhD in Life Sciences from the Department of Molecular Microbiology and Biotechnology, Faculty of Life Sciences and his MBA from the Leon Recanati Graduate School of Business Administration both at the Tel Aviv University, Israel.

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