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Modulated electro hyperthermia inhibits tumor progression in a triple negative mouse breast cancer model

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Published Online: 1 Apr 2019 | **Abstract Number:** 802.42

Abstract

Introduction

The effective therapy of triple-negative breast cancer (TNBC) has not yet been achieved. Modulated electro-hyperthermia (mEHT) is a novel adjuvant antitumor therapy, based on the highly selective heating of the tumor tissue by a 13.56 MHz radiofrequency current induced electric field.

Aims

Our aim was to investigate the effects of repeated mEHT treatment in a triple-negative mammary carcinoma bearing mouse model.

Method

4T07 cells were inoculated orthotopically in female BALB/c mice. Tumor growth was monitored in vivo by digital caliper and ultrasound (Phillips Sonos 5500). The mEHT (n=8) or sham (n=9) treatments started 7 days after inoculation and were repeated 5 times, on every other day. Mice were euthanized 1 day after the fifth treatment and the tumors were dissected, weighed and processed for histology and molecular biology techniques. The ratio of the damaged area compared to the whole tumor area (Tissue Destruction Ratio, TDR) was evaluated on H&E and cleaved caspase-3 stained sections, while HSP70, a common damage-associated molecular signal, Ki67, a proliferation marker and p21, a tumor suppressor protein expression were analyzed on immunohistochemical staining with the HistoQuant module of the CaseViewer Software (3DHistech).

Results

There was a significant decrease in tumor growth (sham: 5.7x, mEHT: 2.4x relative to pre-treatment (day 6) size, $p<0.0001$) and weight (sham: 288.3±58.1 mg vs mEHT: 85.3±21.3 mg, $p<0.05$) in the mEHT treated group, compared to the sham group. The HSP70 stained area in the non-destructed tumor tissue was 5.2 fold higher in the mEHT treated group, compared to the sham group ($p<0.05$). Moreover, the Ki67 positive nucleus / mm^2 count was significantly lower (sham: 2823.4±211.9 pcs/mm^2 vs mEHT: 1736.7±315.3 pcs/mm^2, $p<0.05$) and the p21 positive nucleus / mm^2 count showed increasing tendency (sham: 127.0±25.3 pcs/mm^2 vs mEHT: 242.2±78.2 pcs/mm^2, p = 0,073) in the mEHT treated group, compared to the sham group.

Conclusion

Our findings suggest, that repeated mEHT could lower tumor cell proliferation by promoting cell cycle arrest in vivo. Thus, mEHT could be a possible alternative adjuvant therapeutic strategy for TNBC cancer patients. We plan next generation sequencing to elucidate the biological mechanism behind the effects of mEHT.

NVKP_16-1-2016-0042

This abstract is from the Experimental Biology 2019 Meeting. There is no full text article associated with this abstract published in *The FASEB Journal*.

Vol. 33, No. 1_supplement
April 2019

Publication History

Published online 1 April 2019