Modulated electro-hyperthermia in combination with heat shock response inhibitors significantly increase tumor cell death

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Citation: Danics L. et al. (2020): Modulated electro-hyperthermia in combination with heat shock response inhibitors significantly increase tumor cell death, Oncothermia Journal 29: 110 – 115,
www.oncotherm.com/sites/oncotherm/files/2021-02/Danics_Heatshockresponse

Abstract

Breast cancer is one of the most frequent cancer types among women worldwide. Triple-negative breast cancer (TNBC) is a highly aggressive type with very poor survival due to the lack of targeted therapy. Here we tested the efficiency of mEHT treatment alone and in combination with heat shock response (HSR) inhibitors in the 4T1 mouse TNBC isograft model. Tumors were treated with ergonomic pole electrode and LabEHY 200 device at 0.7 ± 0.3 W for 30 min every 48 h. Tumor growth was followed by IVIS, caliper, and ultrasound. Tumor destruction histology and molecular changes using immunohistochemistry and RT-qPCR were also revealed. In vivo, mEHT treatment transitionally elevated Hsp70 expression in surviving cells indicating heat shock-related cell stress, while IVIS fluorescence showed a significant reduction of viable tumor cell numbers. Treated tumor centers displayed significant microscopic tumor damage with prominent signs of apoptosis, and major upregulation of cleaved/activated caspase-3-positive tumor cells. Serial sampling demonstrated substantial elevation of heat shock (Hsp70) response 12h after the treatment which was exhausted by 24h after treatment. Heat shock inhibitors Quercetin or KRIBB11 could synergistically amplify mEHT-induced tumor apoptosis in vitro. In conclusion, modulated electro-hyperthermia exerted a protective heat shock response as a clear sign of tumor cell stress. Exhaustion of the HSR manifested in caspase-dependent apoptotic tumor cell death and tissue damage of triple-negative breast cancer after mEHT monotherapy. Combined therapy with HSR inhibitors synergistically increased the effect of mEHT, which finding has great translational potential.

Grant support: NVKP_16-1-2016-0042

38th Conference of the International Clinical Hyperthermia Society

The 5th of November 2020

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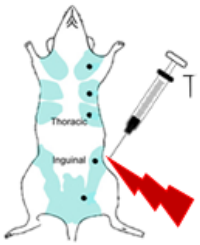
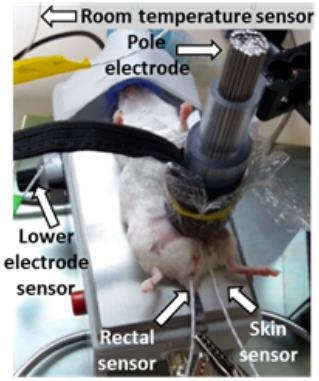
PROTOCOL

♀ Balb/C mice



10^6 4T1 TNBC cells

2 × mEHT Label HY-200 40°C 30min



SAMPLING

24h post-treatment

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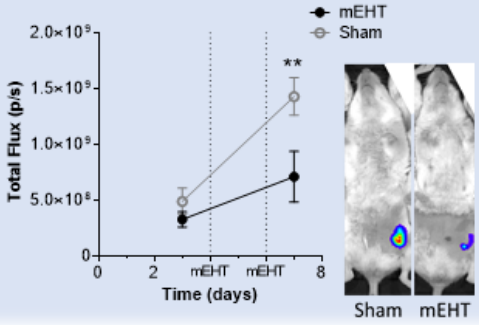
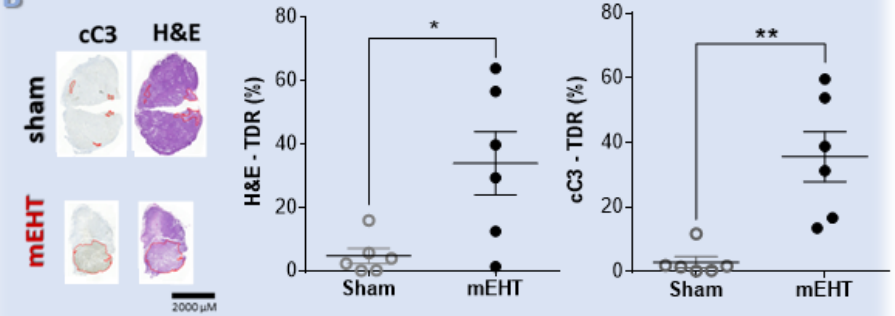
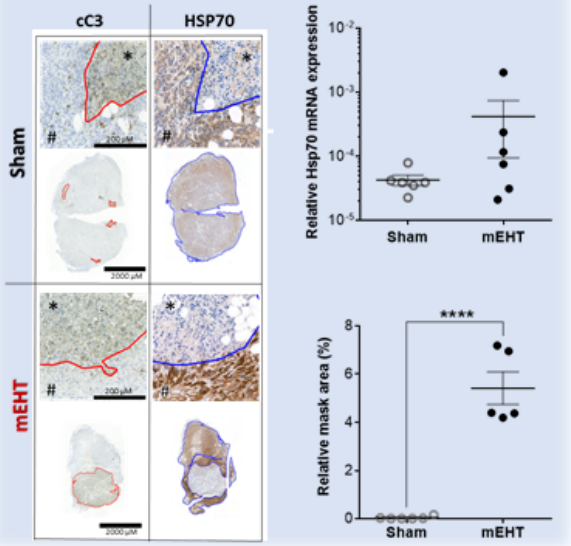
A In Vivo Imaging of viable tumor cells



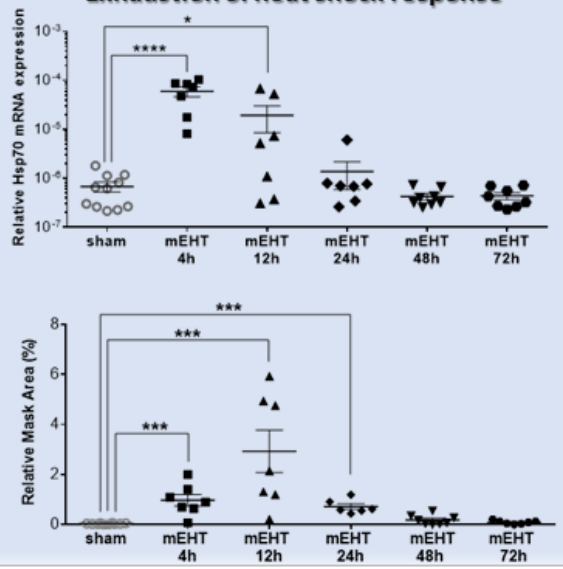
B Tumor Destruction Ratio



C Heat shock response (HSR)



D Exhaustion of heat shock response



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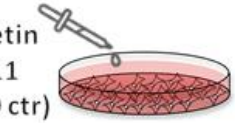
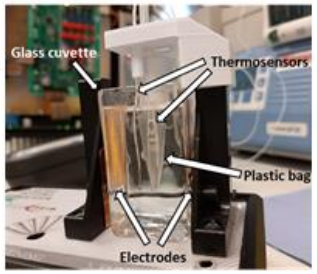
PROTOCOL

1 CULTURING
4T1 TNBC cells

2 INCUBATION
with HSR inhibitors
Quercetin
KRIBB11
(DMSO ctr)



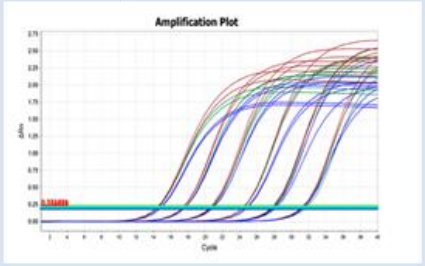
3 TREATMENT
LabEHY-200
42°C 30min

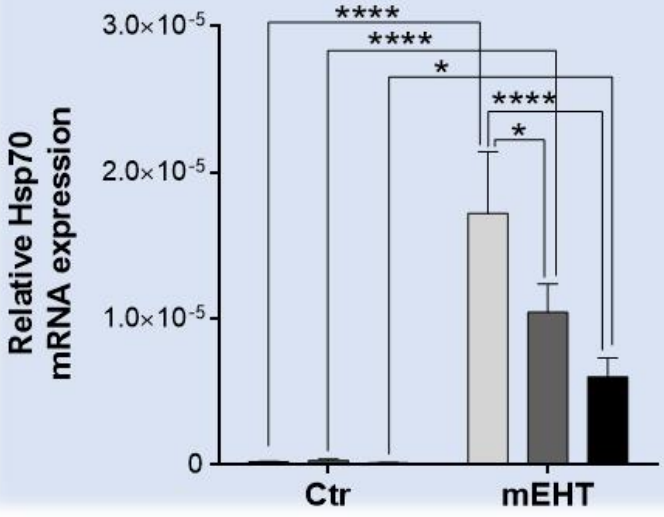


4 SAMPLING & ANALYSIS

A Hsp70 RT-qPCR

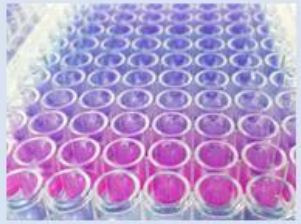
2h post-treatment

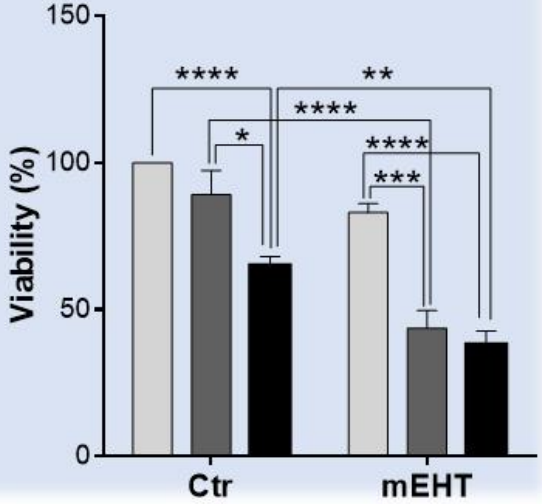




B Resazurin viability assay

24h post-treatment





DMSO (0.1%) Que (50uM) KRIBB11 (5uM)

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CONCLUSIONS

- Repeted mEHT resulted in significant tumor destruction in vivo
- mEHT induced roboust Hsp70 elevation
- Hsp70 response was exhausted at 48 hours after treatments
- **Inhibition of heat shock response potentiates the therapeutic effect of mEHT**

Thank You for Your kind attention!

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Grant support: NVKP-6-1-2016-0042