

Local treatment with systemic effect

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Local treatment with systemic effect

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Objective

Most of the radiation therapies are local. The local control of the tumor in advanced cases is not enough for effective improvement of survival time, due to the systemic malignant spread forming macro and micro metastases which are the main life-threatening factor of cancerous diseases. The local treatment has to be extended by systemic (abscopal) effect. The appropriate immune-stimuli could extend the local method to systemic and acts disseminated cells in distant metastases, too. Our objective is to present the abscopal effect of modulated electro-hyperthermia (mEHT, oncothermia).

Methods

Non-ionizing radiofrequency (RF) electric current amplitude modulated by the time-fractal technique of relative low carrier frequency (13.56 MHz) is used [1]. The E-class RF-source and the impedance controlled capacitive coupling allows high efficacy targeting selectively the membrane rafts of the malignant cells [2]. The applied nano-selection makes certain deviations of cellular metabolic-processes of malignant cells. The cell-killing mechanism is connected to the nano-range energy absorption. The special process makes it available to present the genetic information of malignant cells to the antigen-presenting cells (APCs). There were various in-vitro and in-vivo immune-histochemical studies proving the selection and its effects.

Results

The method of mEHT causes significant apoptotic tumor-cell death. Mitochondrial Bax and release of Cytochrome C and nuclear translocation of apoptosis inducing factor AIF are measured [3], showing caspase independent and also excited caspase dependent pathways of the signal processes. Immunohistochemistry and apoptosis protein array proved elevated hsp70 and hsp90 expression and release them from the cell. The process forms damage associated molecular pattern (DAMP) concluding to immunogenic cell-death (ICD). The abscopal effect is proven by the in-vivo experiment using an intratumoral dendritic cell (DC) injection together with the mEHT for C3H/He mice inoculated with tumor in femoral region. The non-treated tumor in the abdomen was measured. The whole body antitumor effects are proven, [4]. Furthermore, mEHT plus DC administration significantly inhibits the CT26 tumor growth in BALB/c mice, while even the re-challenging of the tumor inoculation became impossible, [5]. In this case the abscopal effect works like vaccination. The combined mEHT-DC treatment increases the myeloperoxidase concentration and CD3+ cells organizing specific T-cell response, [6].

Conclusion

mEHT induces abscopal effect by immune involving processes. Unlike conventional homogeneous heating of the tumor, this local treatment becomes systemic in consequence of the selective excitation of membrane rafts inducing DAMP and ICD. This way mEHT can

create a favorable tumor microenvironment for an immunological chain reaction which improves the success rate of intratumoral dendritic cell immunotherapy

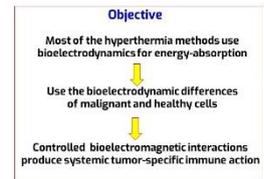
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- 2 Andocs G. et.al. *Biol and Med*, 7(4):1-9; 2015
- 3 Meggyeshazi N. et.al. *Strahlenther Onkol*, 190:815-822; 2014
- 4 Qin W et.al. *Oncol Rep* 32:2373-2379; 2014
- 5 Tsang Y-W et al. *BMC Cancer* 15:708; 2015
- 6 Meggyeshazi N. Ph.D. theses, Semmelweis University, 2015

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INTRODUCTION (malignancy is systemic)

Most of the radiation therapies are local. The local control of the tumor in advanced cases is not enough for effective improvement of survival time due to the systemic malignant spread forming macro and micro metastases, which are the main life-threatening factors of cancerous diseases. **The local treatment has to be extended by systemic (abscopal) effect.** The appropriate immune-stimuli could extend the local method to systemic and acts disseminated cells in distant metastases, too. Our objective is to present the abscopal effect of modulated electro-hyperthermia (mEHT, oncothermia).

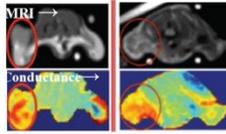
METHOD (precise selection of targets)

Non-ionizing radiofrequency (RF) electric current amplitude modulated by the time-fractal technique of relative low carrier frequency (13.56MHz) is used [1].

Selection by

1 Electric conductivity (Metabolic differences, Warburg effect)

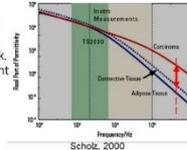
Due to high metabolic rate, the tumor ionic concentration is high and consequently its conductivity selects



Mufluer (2008)

2 Dielectric permittivity (autonomy of malignant cells; Szentgyorgyi effect)

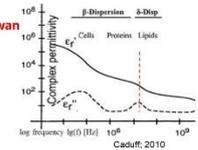
Due to missing cellular network, extracellular matrix of malignant cells have high dielectric permittivity selection



Scholz, 2000

3 β/δ frequency dispersion (lipid resonance absorption; Schwann effect)

Due to large number of clusters of transmembrane proteins the protein-lipid complex is attacked



Caduff, 2010

Technical

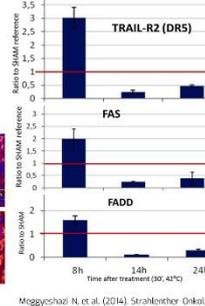
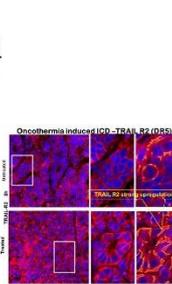
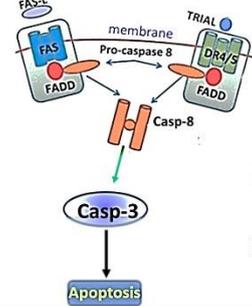
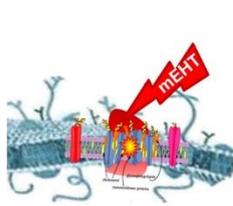
The high-efficacy (E-class) RF-source and the impedance controlled capacitive coupling with a precise control allows to use electric current instead of plain wave radiation allowing high efficacy targeting selectively the membrane rafts of the malignant cells [2]. The precise and automatic tuning makes high efficacy impedance matching and energy absorption, using only 150W maximal power and max. 1-2W reflected one. Due to the step-up heating protocol the average power is 100W/ treatments.

RESULTS

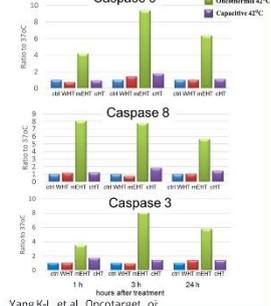
The method of mEHT causes significant apoptotic tumor-cell death. Mitochondrial Bax and release of Cytochrome C and nuclear translocation of apoptosis inducing factor AIF are measured [3], showing caspase independent and also excited caspase dependent pathways of the signal processes. Immunohistochemistry and apoptosis protein array proved elevated hsp70 and hsp90 expression and release them from the cell. **The process forms damage associated molecular pattern (DAMP)** concluding to immunogenic cell-death (ICD). The abscopal effect is proven by the in-vivo experiment using an intratumoral dendritic cell (DC) injection together with the mEHT for C3H/He mice inoculated with tumor in femoral region. The non-treated tumor in the abdomen was measured. The whole body antitumor effects are proven. [4]. Furthermore, mEHT plus DC administration significantly inhibits the CT26 tumor growth in BALB/c mice, while even the re-challenging of the tumor inoculation became impossible. [5]. In this case the abscopal effect works like vaccination. The combined mEHT-DC treatment increases the **myeloperoxidase concentration** and CD3+ cells organizing specific T-cell response. [6]. The time-fractal modulation chooses special processes for immunogenic reactions. The applied nano-selection makes certain deviations of cellular metabolic-processes of malignant cells. The cell-killing mechanism is connected to the nano-range energy absorption. The special process makes it available to present the genetic information of malignant cells to the antigen-presenting cells (APCs). There were various in-vitro and in-vivo immune-histochemical studies proving the selection and its effects.

Excite membrane rafts (extrinsic pathways of apoptosis)

Excitation of transmembrane proteins induces caspase dependent and caspase independent pathways apoptosis became active



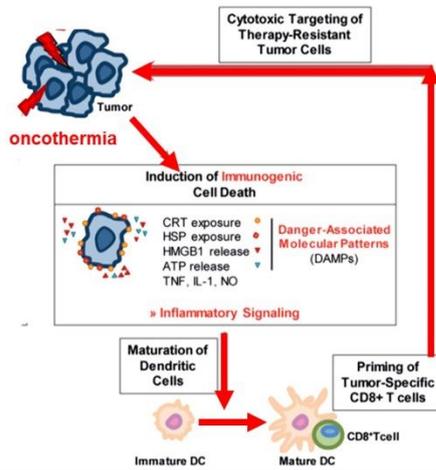
Meggyeshazi N. et al. (2014) Strahlenther Onkol. 190:815-822



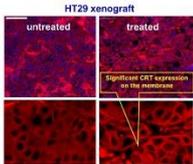
Yang K-L. et al. Oncotarget. doi:10.18632/oncotarget.11474

Produce DAMP and ICD Forming a tumor-specific immune reaction, like vaccination

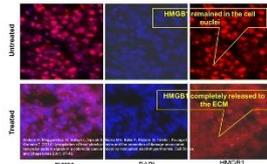
Ando G. et al. (2014) Cell Stress and Chaperones 20(1):37-46



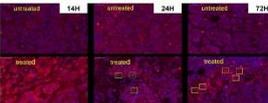
CRT „eat me“ signal



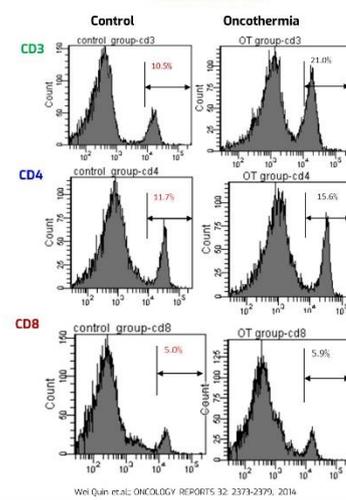
HMGB1 „danger“ signal



Extracellular HSP70 „info“ signal



Result of FACS



Wei Qian et al. ONCOLOGY REPORTS 32: 2373-2379, 2014

CONCLUSION

mEHT induces abscopal effect by immune involving processes. Unlike conventional homogeneous heating of the tumor, this local treatment becomes systemic in consequence of the selective excitation of membrane rafts inducing DAMP and ICD. On this way mEHT can create a favorable tumor microenvironment for an immunological chain reaction which improves the success rate of intratumoral dendritic cell immunotherapy. Research for the role of exosomes and other small vesicles in the abscopal effect and the crosstalk between the primary and metastatic lesions is in progress.

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