Effects far from equilibrium in electromagnetic heating of tissues

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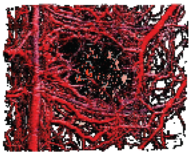
Objective

One of the very first treatment "technologies" for oncology is the regional heating of the tissues and body parts, (hyperthermia, HT) This long history was not enough to be accepted as conventional treatment, facing mostly skeptic opinions among the oncology experts The main reason is its controversial results and poor control, the missing of appropriate selective, controllable safe deep heat delivery Constrained balance of physiological feedback and the sophisticated transport network with very heterogenic tissue structures block applying the simple heating practices This situation requests definite bioengineering tasks as well as new paradigm for the medical applications The modern heating technologies based on electromagnetic interactions made a huge step ahead in this complex field, but not enough yet to solve some crucial problems in deep heating [1] The commonly applied microwave and high radio frequency (RF) radiation is challenged by the magnetic and capacitive heating techniques, applied lower frequencies oncothermia method (OTM), heats by the dielectric loss in the various body electrolytes and makes possible to select between the tissues and concentrate on the malignant cells Due to the constrained RF current conduction of oncothermia, the complex impedance determines the actual flow direction of the current This could distinguish by the microscopic heterogeneity in the treated tissue [2] The main problem is the temperature, which would like to equalized by time in the heated area, and steadily heats up the full environment in wider and wider range, supplying the tumor for growth We need energy input which can be focused and has no physiologic control This is which oncothermia had introduced

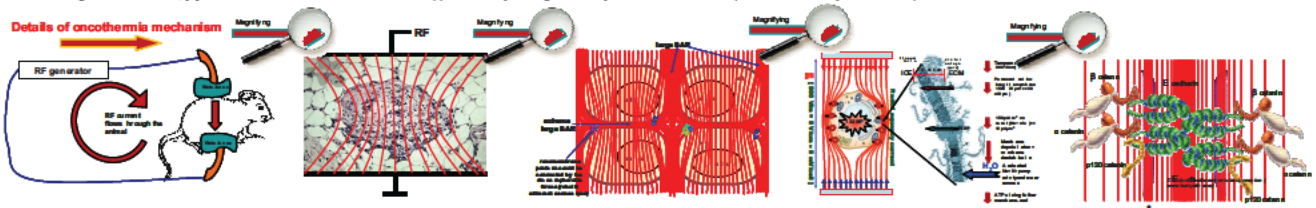
Oncothermia solves the problem: selectively forces various pathways of apoptosis by electric field



By time the temperature equilizes in the area, the heat is conducted away

Method

The relatively low frequency RF current dominantly flows in the extracellular electrolyte The energy absorption creates a temperature gradient through the cellular membrane, which drives non equilibrium processes by constrained heat flow through the membrane, [3] The ion and mass flows could be well approached by Onsager's theory in the frame of non equilibrium thermodynamic description



Oncothermia arrangement (capacitive coupling) [oncothermia]
Tumorous experimental animal is a part of the electric circuit, well controlled, unharmed, anesthetized

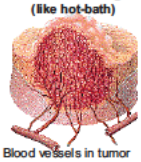
Current density in tumor (Impedance selection)
Low impedance of tumor focuses the RF current and its energy in the highly proliferating volumes

The impedance and so the SAR is not homogeneous
The extracellular electrolyte has lower impedance and higher current density, more absorption

Cell-membrane is damaged or modified to more permeable
The temperature gradient is a driving force of non equilibrium effects (Onsager's cross flows)

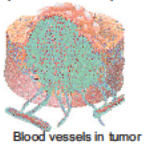
The adherent proteins are reoriented and connected
The adherent connections and many "social" pathways are reconstructed for function

Surface heating (like hot-bath)



Blood vessels in tumor are the heat sources

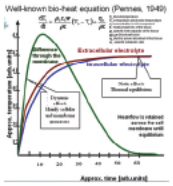
Deep heating (like oncothermia)

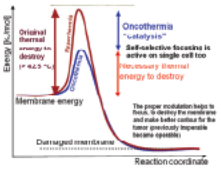


Blood vessels in tumor are the heat sinks (!)

The actual realization of oncothermia is capacitive coupled heating, using the constrained conduction of 13 56 MHz RF [5], amplitude modulated by time fractal pattern [6], which is not limited by the thermal energy [7]

In vitro and *in vivo* experiments were accomplished on identical 42 °C reference temperature by conventional hyperthermia and oncothermia methods, respectively The experimental systems are *in vitro* cell lines (HT29, B16, HepG2, A431) and their *in vivo* xenografts in nude mice The changes of the adherent connections the cell membrane associated effects (activation of the apoptotic signal transduction pathways, heat shock protein mediated stress responses) were studied *in vitro*, while the cell destruction mechanisms were investigated *in vivo*





Results

Synthesis of HSP-s additional extracellular and membrane HSP70 appears through the more permeable membrane

$T_o + \Delta T$, $\Delta T \approx 0{,}01$ °C/10 nm ≈ 10^6 °C/m, Temperature-gradient driven processes

Thermo-electrical current ≈ 150 [pA/μm²] (Na^+ influx), normal ≈ 12 [pA/μm²] Na^+ efflux}, drastically decreases the membrane potential, destabilizes the membrane

Thermo-mechanical pressure ≈ 1320 kPa, (electro osmotic effect, rigid tumorcell membrane), water pressure

Heat flow ≈ 1 5 [pW/μm²] (at 1 [K/s]), (metabolic heat flow ≈ 0 002 [pW/ μ m²], destroys the ordered membrane

Rectifying effect leads a positive feedback to gain the temperature and the pressure in the membrane

Specific absorption rate of water is high in the membrane (Beta dispersion, ~10 MHz)

Membrane associated apoptotic pathways are activated (E cadherin, beta catenin, p53 expression)

Oncothermia paradigm avoids from high temperature, because:

- Temperature heats up the vicinity of the tumor, it can not kept locally focused
- Temperature increases the danger of burn of healthy parts in depth (misfocusing, conduction, etc)
- Temperature request the increase of the safety cooling on the skin
- The increased surface cooling blocks the temperature sensing in the skin,
- The increased surface cooling makes the skin even more isolating, and so the electric burn is more likely
- Temperature increases the blood flow in the region, in consequence increases the dissemination
- In complementary application with radiotherapy the forced high temperature suppresses the efficacy or blocks at all the effect of radiotherapy
- In complementary application with chemotherapy the forced high temperature suppresses the efficacy or blocks at all the chemopenetration into the tumor (vasocontraction or blood vessel blockage in the tumor)
- In complementary application with chemotherapy the forced high temperature increases the cytotoxic side effects in the heated healthy tissues around by increased chemo reaction rates (vasodilatation in the healthy tissues)
- The toxins from the necrotic cells are rapidly transported into the whole body, challenging the anyway low immune status of the patient

In oncothermia the temperature is not a correct dose control, because:

- Moderate temperature avoids the natural contra regulation effects
- Temperature does not exceed the systemic physiological limit (42 oC)
- Tumor selection is solved by non temperature dependent way (electric concept)
- Focus is to be fixed to the tumor, moves together with the natural body movements (impedance control)
- Selection is solved on cellular level suppress the dissemination of the malignant cells
- Cellular connections (adherent connections, gap junctions) of malignant cells are reestablished to avoid the further dissemination
- Cellular communications (social signal) is reestablished to promote the natural (programmed) cell death for malignant cells
- Possibility of the cellular molecular exchange (gap junctions) is reestablished to promote the normal function of the cells
- The "master switch" (p53 gene) is activated promoting the natural way of various cell killing pathways
- Cell membrane permeability is increased to express the HSP on the outer membrane signalizing the cell malignancy for the systemic immune actions
- Cell membrane is excited to ignite various communication pathways in the cells
- Electric field blocks the positive feedback loop of tumor supporting injury currents

Oncothermia avoids the static approach

- Measurement of intensive thermodynamical parameters (like temperature) supposes at least local equilibrium, which never could be realized due to the intensive contra regulatory effects (This concept however, became the main request of the classical hyperthermia approach in its guide lines)
- The forced equilibrium increases the heat flow to the blood stream, which is an effective cooling media trying to block the static concept
- The heat flow to blood supports the positive feedback loop of the basic acidic electrolyte balance, and promotes the intensive growth of the tumor by addressed oxygen delivery
- Static constrains try to block the natural dynamism of the living system, which mobilizes its forces to keep the dynamic equilibrium instead of the static one This creates protection mechanisms of the actual status quo in the tissue, defending the tumor instead its elimination (These processes like intracellular HSP development, like forced delivery of metabolic species [oxygen and nutrition], like systemic cooling control, like various stress reactions, etc)
- Process reaching equilibrium mobilizes higher level of physiological contractions and accelerates a competition between the constrains and the nature This falsely mobilizes the natural healing forces (Natural actions are gained against the actual treatment and not against the "common enemy", against the malignancy)

Oncothermia works with entirely dynamic (natural) processes

- Oncothermia uses tumor killing approach, which is well fitted to the dynamism of the living system, does not constrain it for false defense
- Control of oncothermia is natural, always fitted to the actual conditions (changes of the electrolytes determines its actions)
- No considerable heat flow to the blood stream by oncothermia, no gain of the positive feedback of electrolyte balancing loop
- Thermal gradients make dynamism in a very local area of the cell membrane of malignant cells The applied selection focuses on this thermal non equilibrium
- The relatively slow "step up" heating keeps the non equilibrium stable for long time for action
- The slow heating up does not create considerable physiological contra actions,
- The slow heating makes the healthy tissue adapted to the growing temperature
- The slow temperature change does not generate high stress and following stress reactions
- The applied electric field makes at least three time more effective cell killing than the temperature does
- The applied fractal modulation makes possible selecting and supporting the natural processes to activate the natural healing mechanisms and reestablish the healthy "social signal" between the isolated cells, promoting the anti malignancy coactivity
- Complete relaxation could be supported by relaxing music, video or sound effects during the treatment

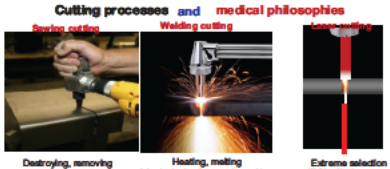
Oncothermia is f personalized

- Oncothermia is mainly regulated by the patient's tolerance
- Oncothermia control based on thermal sensing of the patients, for safety and for efficacy reasons Safety is avoid burning he tissue of the subcutaneous layers, the efficacy to apply such energy, which does not overload the patient natural defending/protective system
- Oncothermia uses natural processes to cure, understa nding and using these needs hinking doctors and their understandings
- Oncothermia acts of natural physiology regulation, which needs understanding of he processes
- Oncothermia needs permanent dynamic approach, follow up we l what is happening during the treatment
- Step up heating is the basic treatment approach, which requests permanent care on the process
- The effect of the activated natural processes are not acting immediately To have a control treatment by treatment is essential
- The patient's well being during and after he treatment is necessary side of the well conducted protocol
- Complete relaxation could be supported by relaxing music, video or sound effects during the treatment

Conclusion

The non equilibrium thermodynamics makes OTM feasible to go over the difficulties of the problem of the selective deep heating With this new paradigm OTM could be a candidate in the branch of modern therapies in medical practice OTM could be applied in various biomedical fields where the selection and the drug targeting as well as the personalized treatment are important requests

Cutting processes and medical philosophies



Destroying, removing
No heating cutting removing by mechanical work
Philosophy of Surgery
Removal, wound
Optical orientation

Heating, melting
Intensive heating for sawing also making deformation and resolving in the material
Philosophy of Hyperthermia
Burn out, necrosis
Thermal orientation

Extreme selection
Well localized energy consumption very precise
Philosophy of Oncothermia
Activation of apoptosis
Modulated electric field

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