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Modulation effect in oncothermia

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Abstract

Conventional hyperthermia is based on the local or systemic heating, which is measured by the realized temperature in the process. Oncothermia applies nano-heating, which means high energy absorption in nanoscopic range of the malignant cell-membrane selectively. This high temperature and its consequent stress create special effects: it evolves possibility of chaperone proteins to be expressed on the outer membrane by softening the membrane, and starts various excitations for programmed cell-death of the targeted malignant cell. The process needs special delivery of the energy which selects as desired. A strict 13.56 MHz sinusoidal carrier frequency is amplitude modulated by time-fractal signals. The modulation is far from any sinus or other periodic patterns, it is a 1/f spectrum, having definite templates for its construction. In some personalized cases definite template is used for fractal pattern, which is copied from the actual character of the tumor-pathology or other specialty of the target.

Keywords: modulation, radiofrequency, hyperthermia, oncothermia, pink-noise, 1/f-spectrum, timefractal, apoptosis

Introduction

The understanding the principle of modulation starts with a simple everyday task: listening our favorite radiobroadcasts, like 107.1 MHz Cologne, 91.8 MHz Frankfurt, Radio Energy (Munich) 93.3 MHz etc. We choose the frequency (tune the radio to select it) and we enjoy the broadcast. The carrier frequency which was the basic of the tuning never meets the ear, it is too high for sensing, and anyway it would be a too monotonic sound, it is only a single frequency. Instead of monotony we hear the music or other information carried by this chosen frequency. The carrier-frequency delivers the real information coded in its modulation (see Figure 1.).

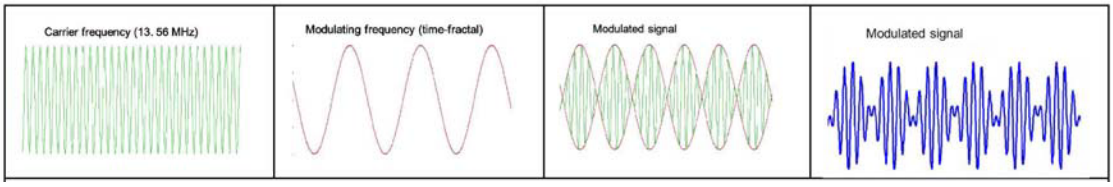

Figure 1. The amplitude modulation. Carrier frequency (a), modulation signal (b), modulated signal shown the frame of the modulator (c), modulated signal alone (d)

The carrier frequency carries two important information characters:
- its modulation finds the target on cellular level and
- its energy heats up the selected cells from outside by its neighboring extracellular matrix.

The modulation method is similar to the process when the light goes through the windows-glass. When the glass is transparent to that specific set of colors (visible light, definite interval offrequencies), its absorption is almost zero, all energy goes through it. However, when it has any bubbles, grains, precipitations, etc., those irregularities will absorb more part from the energy, their transparency will be locally low, their energy absorption will be high, they will be heated up locally. It is a self-selection depending on the material and the frequency (color) which we apply in the given example. The carrier frequency delivers the information (modulation frequencies), for which the cancer cells are much less "transparent" than their healthy counterpart is. Malignant cells are heated up by the selectively absorbed energy.
The applied time-fractal modulation is one of the specialties, which only oncothermia has in hyperthermia applications in oncology.

Method

The living material is not an ordered solid. Contrary to the crystals, it is hard to introduce the cooperativity. The living matter is in aqueous solution, which is mostly well ordered, [1] in the living

state. This relative order formed the "dilute salted water" into the system having entirely different mechanical, chemical, physical, etc. behaviors as the normal aqueous solutions. Indeed, the important role in the living systems of the so called ordered water was pointed out in the middle of sixties, and later it was proven, [2]. At first the ordered water was suggested as much as 50 % of the total amount of the water in the living bodies [3]. The systematic investigations showed more ordered water [4], [5] than it was expected before. Probably the ordered water bound to the membrane is oriented (ordered) by the membrane potential, which probably decreases the order of the connected water, so increases the electric permeability of the water [6], and so decreases the cell-cell adhesion and could be the cause of the cell-division of even for the proliferation [6]. According to Warburg's effect the metabolism gradually favors the fermentation in malignancy [7]. The end-products of both the metabolic processes are ions in the aqua-based electrolyte. The oxidative cycle products dissociate like 6CO2+6H2O 9 12H+ + 6CO32- while the lactate produced by fermentation dissociates: 2CH3CHOHCOOH 9 2CH3CHOHCOO- + 2H+. Assuming the equal proton production (by more intensive fermentation energy-flux) the main difference is in the negative ions.

The complex lactate-ion concentration grows rapidly, and increases its osmotic pressure. Keep the pressure normal, the dissolvent (the monomer water) has to be increased as well, seeking to solvent by non-ordered water. Indeed, it is measured in various malignancies that the water changed to be disordered, [8], [9], [10], so in these cases the ordered water concentration in cancerous cells is smaller than in their healthy counterpart. Consequently, the hydrogen ionic transmitter became weak, the removal of the hydrogen ions became less active. This decreases the intracellular pH and the proton gradient in mitochondria, which is directly worsening the efficacy of ATP production. To compensate the lowered proton-gradient, the membrane potential of mitochondria grows. This lowers the permeability of the membrane, decreases the mitochondrial permeability transition, which have crucial role in apoptosis, [11], [12]. (The high mitochondrial membrane potential and low K-channel expression had been observed in cancerous processes, [13]). These processes lead to apoptosis resistance, and for the cell energizing the ATP production of the host cell (fermentation) became supported. The free-ion concentration increases in the cytoplasm, and so the HSP chaperone stress proteins start to be produced. This process needs more ATP as well as it is anti-apoptotic agent, so the process could lead to the complete block of apoptosis. Rearranging (disordering) the water structure needs energy [14]. It is similar to the way, like the ice is melted with latent heat from zero centigrade solid to liquid with unchanged temperature conditions. This drastic change (phase transition) modifies the physical properties (like the dielectric constant) of the material without changing the composition (only the microscopic ordering) of the medium itself.

The decisional role of the two metabolic pathways (the oxidative and the fermentative) was studied by Szent-Gyorgyi [6], having etiology approach, and using additional formulation. His interpretation describes the cellular states by two different stages. The alpha-state of the cell is the fermentative status.

What makes the difference on the absorption? It is the missing collective order in malignancy. The healthy cells live collectively. They have special "social" signals [15] commonly regulating and controlling their life. They are specialized for work-division in the organism, and their life-cycle is determined by the collective "decisions". The cancerous cells behave non-collectively; they are autonomic. They are "individual fighters", having no common control over them, only the available nutrients regulate their life. The order, which characterizes the healthy tissue, is lost in their malignant version, the cellular communications disappeared [16].

The problem of the autonomy of the malignant cells makes the treatment very much complicated, because cancer has its own fractal structure, [17]. The analysis of the fractal structures of malignancies could even indicate the stage of the disease [18]. Careful fractal analysis can make predictive information for the prognosis as well, [19].

Results

The effect of modulation was measured on immuno-deficient nude mice xenograft model made by HT29 human colorectal carcinoma cell-line. The single shot oncothermia was used for 30 min keeping 42 °C in the tumor. A day after oncothermia a definite difference can be detected between the modulated and unmodulated effects, which became very emphasized after two days, (see Figure 2. [20]). This is one of the reasons, why we propose in the protocols of oncothermia the treatment frequency every other day.

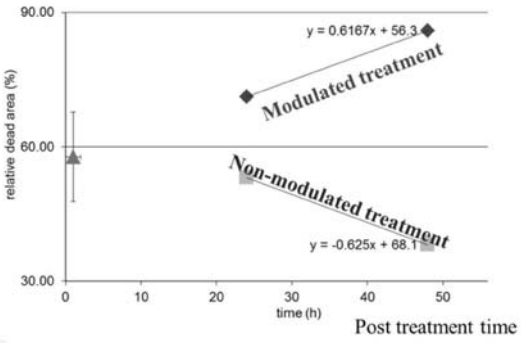

Figure 2. The modulation reestablsihes the apoptosis, the natural cell-killing process, and after 48 h the effect is obviously acting. (HT29 xenograft model on single-tumor-bearing mice, heating single shot, 30 min to 42 C. Animals were sacrificed 24 h after the treatment.)

The multiple fractal physiological proofs are extended by the oncothermia specialized experimental results too. We used the same xenograft model on a high number of nude mice (30 tumors were examined, 5-5 mice having double tumors in two arms, modulated (active) arm and non-modulated (passive arm)). The single shot experiment was also for 30 min, but the tumors were treated only on 40 °C. We know it from other experiments that this temperature is generally not enough to make hyperthermia effect in classical heating approach. The animals were sacrificed after 48 h, and the results (see Figure 3.) show well the modulation effect: the treated arm in modulated cases had 45.8% higher cell-distortion than the non-treated part, while the effect in the non-modulated mice was only 3,9%.

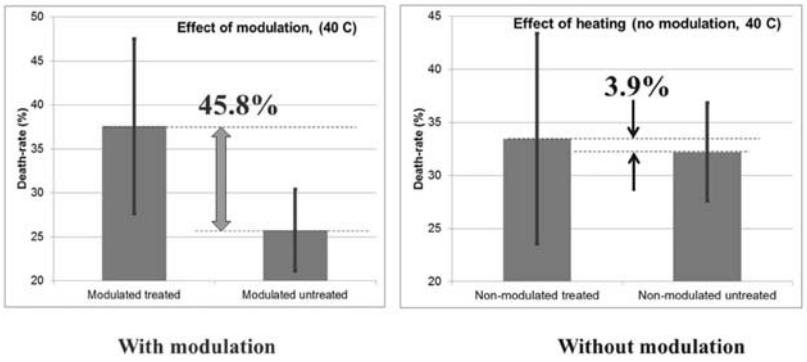

Figure 3. The modulation makes definitely and significantly higher tumor-destruction compared to the non-treated side than the non-modulated cases. (HT29 cell-line in nude mice, xenograft model, single shot for 30 min keeping at 40 C, 5-5 mice were used in both arms, sampling was taken 48 h after the treatment

More detailed explanation and background of the modulation applications in Oncothermia could be obtained from the Oncothermia book [21]. The modulation method has patent applications [22], [23], [24].

Conclusion

Oncothermia modulation is one of the three specialties of this treatment. Its efficacy and its role in the personalization process have introduced an effective tool for the apoptotic cancer-cell destruction.

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