Cancer Physics

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Abstract – **Most important physical processes in living cells depend on mitochondrial function. Mitochondria transfer protons across the inner membrane, generate a strong electrostatic field in the cell (and thus create additional conditions for water ordering in parallel with interfacial ordering), produce ATP and GTP, and liberate non utilized energy. Therefore, normal mitochondria contribute to nonlinearity in microtubules, provide their low damping, and sufficient excitation of electrically polar coherent oscillations. Generated electromagnetic field may perform organization, transport, interactions, and information transfer. The majority of cancer cells display glycolytic phenotype. Mitochondria are dysfunctional, the electromagnetic field has low power and coherence, and water ordering is diminished. The apoptotic pathway is blocked. Physical mechanisms are disturbed or partially suppressed. Targeting mitochondria for cancer treatment restores physical processes in cancer cells. Dichloroacetate and drugs with similar effects may be effective in treatment of cancers with interruption of the pyruvate pathway in mitochondria.**

Index Terms – **Physical processes in living cells, Glycolytic phenotype of cancer, Warburg effect, Mitochondrial dysfunction, DCA treatment.**

I. INTRODUCTION

For a long time physical processes in living cells have been disregarded as a part of biological activity, in particular generation of the endogenous electromagnetic field. As a result fundamental biological mechanisms were neglected including physical links along the cancer transformation pathway. Warburg effect [1–2], i.e. suppression of mitochondrial oxidative metabolism, was considered to be a secondary process without significant influence on cancer transformation. 80 years after Warburg's discovery the situation changed. The Warburg effect has been revisited. Mitochondria are the boundary entities between chemical and genetic processes on the one hand and physical ones on the other hand. Mitochondria are multifunctional organelles that cannot be reduced to mere energy producers in the form of ATP and GTP (adenosine and guanosine triphosphate). Mitochondria condition physical processes in cells and play a critical role in cell organization and activity. Physical processes in living cell and their disturbances along the cancer transformation pathway will be analyzed.

The main physical forces in biological cells and tissues are very likely of electromagnetic origin as predicted by Fröhlich [3]. Fröhlich formulated hypothesis of nonlinear interactions between elastic and electric polarization fields and spectral energy transformation. He suggested that cancer disturbs electromagnetic processes in cells [4]. Cancer transformation includes links which suppress the power of the endogenous electromagnetic field and its coherence [5–8].

II. MITOCHONDRIA – MULTIFUNCTIONAL ORGANELLES

Mitochondria play a role of "power plants" in cells. They utilize chemical energy supplied to the cell and transform it into a form suitable for metabolic use. Pyruvate and fatty acids are transported into the matrix space, broken down to acetyl coenzyme A (acetyl CoA), the crucial metabolic intermediate. Energy released from acetyl CoA is converted into the electrochemical potential energy of protons transported from the mitochondrial matrix into the intermembrane space (in this way energy is parceled out into small packet to be stored into ATP and GTP). After diffusion through the outer membrane the protons establish a space charge layer around the mitochondrion. The negative charge in the matrix space is balanced by the proton space charge layer. A zone of a strong static electric field is produced. Its intensity was measured by fluorescent particles. At the outer membrane the intensity is of about 3.5 MV/m [9] and is measurable up to the distance greater than 1 μm from the mitochondrion. The mitochondria occupy about 22 % of the cellular volume and the layers of the proton space charge and the static electric field fill up its rest. As a result, cytosol, cytoskeleton, and biological molecules are electrically polarized.

Production of ATP and GTP is driven by the electro-chemical proton gradient across the inner mitochondrial membrane. The total efficiency of ATP and GTP production is greater than about 40 %. The non utilized energy (nearly about 60 %), often denoted as the "wasted" energy, is liberated from mitochondrion in the form as photons in the UV, visible an infrared region, heat, and chemical compounds.

III. WATER ORDERING

The interfacial ordering of water in the cell has to be described before assessment of the effect of the mitochondrial static electric field on water ordering and organization in the cell. In the vicinity of biological molecules and structures water molecules become ordered due to the surface charge at the interface [10–12]. This interfacial ordering of the water molecules may exist in a form of layers parallel to the surface. Different physical properties of the organized water in comparison with the bulk water include higher viscosity, lowered thermal motion of molecules, different pH, and different spectroscopic properties. Separation of charge and solvent exclusion are exhibited by ordered layers of water too. Ordered layers of water at strongly hydrophilic interfaces can extend to a distance of hundreds of micrometers as experimentally disclosed by Zheng et al. [11]. The zones of ordered water are called the clear or exclusion zones. Clear zones 5–20 nm thick are formed around microtubules [13]. An overview on water ordering is in [8].

Basic organization of water in the cell may be assumed to be formed at the charged surfaces (the interfacial ordering). The mitochondria ordering is in priciple similar. The zones of a strong static elecric field and the proton space charge layers spreading throughout the cell volume around mitochondria may provide high- level ordering of water. Water ordering is a crucial phenomenon influencing inner cellular processes, in particular low damping of the cytoskeleton vibration systems.

IV. MICROTUBULES – GENERATORS OF ELECTROMAGNETIC FIELD

The cellular cytoskeleton consists of micro-filaments, intermediate filaments, microtubules, and associated proteins. Microtubules are the main organizers of the cytoskeleton and form a network which is used for mitochondria align-ment in the interphase. The microtubules fulfill conditions for generation of the electromagnetic field with a strong electric component [14–15]. Microtubules are hollow cylindrical polymer structures composed of tubulin heterodimers that are strong electric dipoles. Their dipole moment is greater than 1000 Debye (10^{-26} Cm). Due to nonlinear interactions between elastic and polarization waves energy supplied to microtubule oscillators is transformed from random to coherent form. Oscillations are coherent and generate coherent electromagnetic field. The mitochondrial strong static electric field creates conditions for nonlinear oscil-lations, and the non utilized energy efflux from mitochondria provides energy supply. Besides the non utilized energy liberated from mitochondria, energy is supplied from motor proteins moving along microtubules, and from hydrolysis of GTP to GDP (guanosine diphos-phate) in β tubulins after polymerization. Mitochondria liberating the non utilized energy very likely represent the most important energy supplier. Electromagnetic oscillation modes with wavelengths from acoustic to mm wave region participate in biological activity of cells. Electromagnetic activity in infrared and visible wavebands was experimentally disclosed too. The total space pattern of the generated electromagnetic field depends on the cyto-skeleton structure in the cell. The interphase radial and the M phase mitotic spindle microtubule structure may generate discrete quasi-spherical and axial symmetrical patterns, respectively.

V. PHYSICAL PROCESSES IN CELLS

A schematic picture of physical links of cellular activity based on mutual cooperation of mito-chondia and microtubules in a cell is shown in Fig. 1. A decisive factor conditioning nonlinear properties of microtubules and high level ordering of cytosol water may be the static electric field created by mitochondria. Hy-dration of protons may considerably contribute to formation of ordered water structures too. Non utilized energy efflux from mitochondria represents essential metabolic energy supply for excitation of oscillations and creation of the coherent state in microtubules.

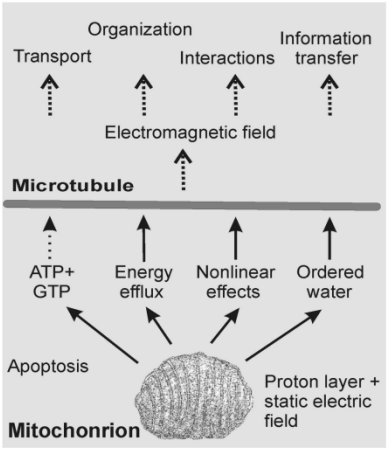


Fig. 1: A schematic picture of physical processes in living cell. The microtubule generates electromagnetic field in a living cell.

Electromagnetic field generated by microtubules seems to be an important agent for cellular activity. The electric field may participate in directed transport of particles and component of chemical reactions, in organization of cellular structures, interactions, and information transfer.

VI. MITOCHONDRIAL DYSFUNCTION IN CANCER CELLS

Suppression of the oxidative metabolism in cancer cells was disclosed by Warburg et. al. and Warburg [1–2]. The majority of cancer cells display suppression of oxidation. Glucose uptake is increased, fermentative production of pyruvate enhanced, and mitochondrial production diminished. Mitochondrial dysfunction is caused by interruption of the pyruvate pathway in mitochondria. Disturbances of mitochondrial function seem to be a general feature of many cancers. Only about one half of the total ATP production is supplied by mitochondria. Warburg assumed that mitochondrial defect has essential consequences on cancer cell development and predicted that „The adenosine triphospate synthesized by respiration therefore involves more structure than adenosine triphosphate synthesized by fermentation“.

Reduction of mitochondrial activity results not only in decreased production of ATP and GTP. Suppression of mitochondrial activity is accompanied by hyperpolarization of inner mitochondrial membrane, diminution of the zone of the static electric field as well as of the layer of the proton space charge layer, and by decrease of the non utilized energy efflux. The apoptotic function is blocked too. Glycolytic phenotype is caused by phosphorylation of PDH (pyruvate dehydrogenase) enzyme family by a cancer kinase [16].

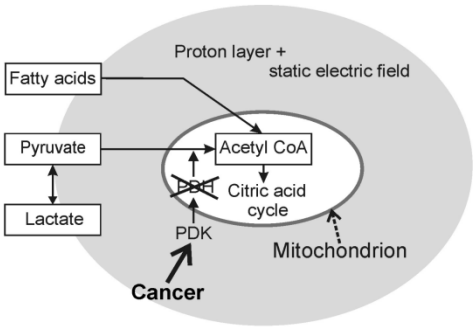


Fig. 2: A schematic picture of glycolytic phenotype of cancer cells. PDK phosphorylates PDH and blocks the pyruvate pathway in mitochondria.

Damping of microtubule oscillations depends on the surrounding medium. Due to decline of the zone of the strong static electric field and of the space charge layer of protons around mitochondria, the high level of water ordering is disturbed and damping of microtubule oscillations is increased [8]. Quality of the microtubule oscillators is considerably impaired. Nonlinear properties of the microtuble systems are weakened, which together with decreased efflux of the non utilized energy from mitochondria leads to small power of electrical oscillations and of the generated electric field, and to decreased coherence. Coherent processes in the cells are disturbed and the random components play more important role. Trans-port is less directed to the target and inter-actions inside the cell as well as between the cells decline to random processes. Due to interaction changes the tissue displays irregular properties and cancer cells may be pulled by healthy cell inside the healthy tissue (local invasion) [17]. Interaction changes based on altered frequency spectrum and spatial pattern of the generated field may apear at the beginning of the metastatic process.

VII. DISCUSSION AND CONCLUSION

Therapeutical strategy of cancer treatment is predominantly based on cancer cell killing. But it is very difficult to find an essential target unique to cancer cells. The differences between healthy and cancer cells are very often slight and of quantitative nature. The treatment may considerably impair healthy cells too. Therapeutic strategy aimed to restore normal cell function through mitochondrial treatment may avoid healthy cell damage and can achieve repair of the apoptotic mechanism [16,18]. Restoration of the normal cell function seems to be more promissing for the future (using DCA or other drugs rebuilding mitochondrial function). But solution of cancer problem

would very likely require combination of different method and drugs

Physical processes are indispensable to biological activity, in particular coherent electromagnetic field. Perturbances and degradation of physical mechanisms are a part of the cancer transformation pathway. Some authors tried to prove that coherent oscillations cannot be excited. But they neglected, for instance, water ordering and analyzed highly damped systems, or disregarded nonlinearity using methods valid in linear systems and constant parameters and coefficients independent of excitation.

A good understanding of biological activity and cancer transformation pathway requires connection of the chemical and genetic processes and mechanisms with the physical ones to build a complete model of biological functions.

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