Electrodynamic activity of healthy and cancer cells

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Abstract. Microtubules in the cell form a structure capable of generating electrodynamic field and mitochondria form their supporting system for physical processes including energy supply. Mitochondria transfer protons from their matrix space into cytosol, create strong static field around them that causes ordering of water and altering it into quasi-elastic medium with reduced viscous damping. Microtubules are composed of heterodimers that are electric dipoles. Microtubule oscillations generate an electrodynamic field. The greatest energy supply may be provided by liberation of non-utilized energy from mitochondria. Microtubules and mitochondria form a unique cooperating system in the cell. Mitochondria form a boundary element whose function depends on chemical-genetic control but their output is essential for physical processes in the cell. Mitochondrial dysfunction in cancer cells results in diminished intensity of the static electric field, disturbed water ordering, increased damping of microtubule oscillations and their shift towards linear region, and decreased energy supply. Power and coherence of oscillations and generated electrodynamic field is weakened. Malignant properties of cancer cell, in particular local invasion and metastasis, may depend on disturbed electrodynamic field. Nanotechnology is promising for investigation of electrodynamic activity in living cells.

1. Introduction

For a long time biological processes and cancer were assumed to be entirely dependent on chemical and genetic changes. In the last decade the attitude has changed. Carew and Huang [1] and Cuezva et al. [2] published papers revisiting the chemical-genetic dominancy and generally accepted opinion that suppression of oxidative metabolism in cancer cells is an irrelevant side effect somehow connected with development of cancer. The oxidative disturbances in cancer cells were disclosed by Warburg et al. [3] and assigned to mitochondrial dysfunction (Warburg [4]). Metabolic imbalances and deficient mitochondrial respiration are described by Kroemer [5] and Brandon et al. [6]. Pedersen [7] claimed that the most striking biochemical phenotype of cancers is their aberrant energy metabolism. Kroemer [5], Brandon et al. [6], and Pedersen [7] papers were published in the special issues of the journal "Oncogene" (2006) and "Journal of Bioenergetics and Biomembranes" (2007) (devoted to mitochondrial dysfunction and the Warburg effect, respectively) which caused the main turn for a real assessment of the Warburg effect. Nevertheless, the mitochondrial function (or dysfunction) was not

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analyzed in connection with physical processes in living cells (or their changes along the cancer transformation pathway).

Since the first Versailles' conference on "Theoretical Physics and Biology" in 1967 the physical mechanisms (in particular of electrodynamic type) were studied, analyzed, and published. H. Fröhlich [8–12] postulated long-range quantum mechanical phase correlations, existence of electrically polar vibration modes excited far from the thermal equilibrium, and generation of endogenous coherent electrodynamic field in biological systems. The main part of the Fröhlich theory is based on the fundamentally non-linear interactions between elastic and electric polarization fields and non-linear spectral energy transformation. The role of disturbances of endogenous electrodynamic processes in cancer transformation was examined, too (Fröhlich [13]). Theory of synergetic operation in systems far from thermodynamic equilibrium was developed and analyzed by Haken [14].

Attraction of dielectric particles to living cells was observed by Pohl [15], Hölzel and Lamprecht [16], and Hölzel [17]. The dielectric particles move along the gradient of the intensity of the electric field towards the region of the greatest intensity (or vice versa), if the difference of their permittivity and the permittivity of the ambient medium is positive (negative). The number of particles attracted to living cells depends on dielectrophoretic forces. The force acting on the dielectric particle is mainly determined by the value of the permittivity difference, the intensity of the electric field and its gradient, and by the conductivity of the suspending liquid. Geometrical shape of the cell (the tip enhanced field effect), and the phase of the cell cycle affects the number of attracted particles too. The greatest number of particles is attracted in the M phase.

Electromagnetic activity of living cells was disclosed in a wide frequency region. Pelling et al. [18–19] measured elastic oscillations at the cellular membrane with amplitude about 3–4 nm in the acoustic band. Measurement of electric and elastic oscillations in the acoustic frequency range (0.4–2 kHz) was performed by Jelínek et al. [20]. Attachment of tubulin heterodimers to microtubule growing end during polymerization may be inhibited by external electromagnetic field in the frequency range 0.1–0.3 MHz (Kirson et al. [21–22]). Transport and correct orientation of heterodimers may be disturbed due to exerted electrodynamic forces. On the basis of theoretical analysis (Pokorný et al. [23–24]) direct technical measurement of the electrodynamic field was performed at the cellular membrane in the frequency range 8–9 MHz (Pokorný et al. [25]). Sahu et al. [26] claims that microtubules in vitro display resonance at the frequency of about 10 MHz. It might be an important discovery of microtubule properties. Increased damping of the power transmitted from an antenna positioned near a malignant tumor was observed at the frequency 465 MHz and its first and second harmonics (Vedruccio and Meessen [27]). The effect was explained on the basis of resonant interaction between external electrodynamic field and intracellular microtubule oscillations. In cancer cells ordering of water is disturbed that causes increased damping (Pokorný et al. [28]).

Interaction between baby hamster kidney (BHK) cells is mediated by electromagnetic field in the red and near infrared region (Albrecht-Buehler [29]). The Swiss 3T3 cells are able to sense the near infrared radiation and to determine direction of individual sources (Albrecht-Buehler [30]). Formation of aggregates of $3T3_x$ cells (a variant derived from 3T3 cells) is conditioned by electromagnetic interaction in the near infrared range (Albrecht-Buehler [31]).

Microtubules in the eukaryotic cells fulfill conditions for excitation of the electrodynamic oscillations. Mitochondria and microtubules are essential cellular parts for cellular electromagnetic activity. This paper analyzes properties of mitochondria and microtubules as the entities conditioning essential physical processes in cells and their disturbances caused by the cancer transformation. The generating structure in the eukaryotic cells is formed by microtubules (Pokorný [32–34] and Pokorný et al. [35–36]).

2. Water ordering by static electric field

Mammalian cell contains about 70% of water. Jellyfish is alive with more than 99% of water. The high content of water in living systems suggests a question about its role in living state and whether water has any special property that makes life possible. Generally, water exists in three phases–

gaseous, liquid, and solid. The physical parameters of the environment (such as temperature and pressure) determine the water phase. Water state (or phase) may depend on other physical parameters too. Damadian [37] explained different NMR (nuclear magnetic resonance) findings on healthy and cancer cells by different level of water ordering in cells in healthy and tumorous tissues. Regions without solutes were observed around microtubules (Amos [38]). These clear regions were suggested to be connected with the negative charge at the microtubule surface (Stebbings and Hunt [39]). Cleveland et al. [40] evaluated NMR measurement with a conclusion that a large fraction of cellular water is associated with the proteins in such a way that its diffusion coefficient is substantially reduced. Some scientists assumed that water may be capable of forming an "ice-like" or "quasi-crystalline" structure. But the idea that water in living cells may have a different physical structure and that living cells are not containers of a bulk water with macromolecules and various organelles seemed to be impossible and, generally, rejected. But water molecules are electric dipoles and external electric field should have strong effects on water behavior. Nevertheless, theoretical assessment of the effect of the external electric field excluded formation of such physical ordered structure (Booth [41]). Regardless of the negative theoretical analysis experimental investigations disclosed water ordering at the surfaces of hydrophilic materials and inside living cells too. The ordered water may be organized in layers around the surface up to a distance of the order of magnitude 0.1 mm. Ling and Murphy [42] used NMR spectroscopy to assess properties of water from measurement of the spin-lattice (T_1) and the spin-spin (T_2) relaxation time of water protons. The T_1 and T_2 relaxation times depend on rotational relaxation time τ_c (characteristic time for rotation of a molecule or time of its diffusion into its next position). Increase of rotational relaxation time by a factor of about 3 (from about 10^{-12} to 10^{-9} s) results in reduction of solvency and produces water that is non-solvent for Na citrate and sulfate. Zheng and Pollack [43] measured exclusion zones using coated latex microspheres in the vicinity of polyvinyl alcohol gels. Exclusion zones about 0.1 mm thick around the surface were observed. A more detailed measurement of exclusion zones were published by Zheng et al. [44]. Probe measurements disclosed negative potential whose difference across the exclusion zone was about 100 mV. UV–Vis absorption spectrum displays a peak at 270 nm in the exclusion zone. This absorption feature was not measured in the bulk water. Infrared emission from the exclusion zone measured by an infrared camera in the spectral window 3.8–4.6 μm is suppressed. The hydrophilic surfaces play a role more profound than generally assumed.

The ordered water at the interfaces may be measured by AFM (atomic force microscopy) as its physical properties differ from those of the bulk water. The ordered water has higher viscosity (Pollack et al. [45]) and lower thermal motion of molecules (Zheng et al. [44]). Different pH (Chai et al. [46]) and different spectroscopic properties (Chai et al. [47]) were found comparing ordered and bulk water properties. Ordered layers of water are remarkable by separation of charges (Chai et al. [46]) and solvent exclusion (Zheng and Pollack [43] and Zheng et al. [44]). Formation of exclusion zones is promoted by infrared radiation (Chai et al. [46]). A more comprehensive set of ordered water properties was published by Pollack et al. [45, 48]. Water ordering may depend on the phase of the cell cycle. Zimmerman et al. [49] found that increased state of ordered water molecules at metaphase is maintained by non-microtubule factors.

The electric field is a general physical agent ordering water. External field can organize water similarly as the electric field at the hydrophilic surfaces. A strong electric field (about 600–700 kV/m) organizes water and forms a floating water bridge about 1–3 cm long between two glass beakers (Fuks et al. [50–52] and Giuliani et al. [53]).

Quantum electrodynamics theory of creation of ordered water was worked out by Preparata [54] and Del Giudice et al. [55]. They found out that the normal "liquid" water is a mixture of two phases. One phase contains coherent domains that form the ordered water regions. The other phase is composed of gas-like water molecules. The exclusion zones are macroscopic structures corresponding to ordered water domains. The coherent domains are reservoirs of quasi-free electrons that may have fundamental impact on biological activity (Del Giudice et al. [55] and Del Giudice and Tadeschi [56]). The exclusion zone structure may represent a transition structure between a liquid and a solid state

material. Protons may diffuse through the exclusion zone and quasi-free electrons may move like electrons in the "conductivity band".

Intramitochondrial water has a high viscosity–30 times larger than the resuspension water (López-Beltrán et al. [57])–that signifies ordered water in the mitochondrial matrix. Bulk solvent water is able to rotate freely, water bound or adsorbed on macromolecular surfaces seems to adopt the correlation time of the host macromolecule. Trombitás et al. [58] observed large water regions near mitochondria and discussed the problem of driving force.

3. Mitochondrial function

Mitochondria are power plants of the cell. Chemical energy stored in pyruvate and fatty acids is parceled out into small parts, transformed into electrochemical proton gradient across the inner mitochondrial membrane, and finally stored into ATP and GTP (adenosine and guanosine triphosphate). Transport of protons into the intermembrane space and their diffusion to the mitochondrial surroundings has essential significance for cellular function. The protons around mitochondria are not only resource of small energy packets but also for formation of a strong static electric field around mitochondria (together with the negative charge in the mitochondrial matrix). Intensity of the static electric field around mitochondria was measured by fluorescence spherical particles 30 nm in diameter (Tyner et al. [59]). The spectrum of the material of the fluorescence particles was dependent on the intensity of the electric field. A zone of a strong electric field is excited around each mitochondrion. At the mitochondrial membrane the intensity of the static electric field is of about 3.5 MV/m. It is measurable even at a distance of several micrometers. As the mitochondria occupy about 22 % of cellular volume the field of different mitochondria may spill over one another. Fluorescent particles may very often measure the field generated by several mitochondria in the vicinity, for instance in the planes below and above the plane of observation. Some experimental results were assumed to be excited only by one mitochondrion and represent the pure cytosolic region. Figure 1 shows the cytosolic intensity of the electric field measured at a mitochondrion at a distance 0.5, 1.0, 1.5, and 2.0 μm (Tyner et al. [59]) and plotted as vertical bars with quadratic regression curve (R). The regression curve has nearly linear dependence on the distance from the mitochondrion (it has a very small quadratic term) which contradicts the theoretical curve (Q) determined from the distribution of the proton space charge around mitochondrion. The intensity values dependent on the proton distribution drop down rapidly near the mitochondrion within a distance of the order of magnitude 10 nm and they are much smaller than the experimental values at larger distances. If the measured intensity actually represents the cytosolic values then water around mitochondrion should be ordered and the proton space charge layer excluded to larger distance. Ordering similar to the interfacial one may be created. The intensity curves of the static electric field of a spherical and cylindrical shape of the exclusion layer model are plotted in figure 1 by short and long dashed curves, respectively. The curve (S2.2) denotes a regression curve of a spherical model for a mitochondrial spherical surface of a radius 2.2 μm.

Protons may be expelled from the exclusion zone and concentrated beyond its distant edge far from mitochondrion membrane. Protons may diffuse into the ordered layer, boundary may be smeared, and the exclusion zone non-uniform. The fact that the exclusion zone of 0.36 mm could be found in 150 mM salt solution argues against a purely electrostatic mechanism (Zheng et al. [44]). Nevertheless, exclusion of protons may depend on the level of ordering. Distribution of the charge depends on its concentration and on the intensity of the static electric field in the exclusion zone. Water ordering alters water from a viscosity liquid to a quasi-elastic gel influencing inner-cellular processes, especially providing low damping of the microtubule vibration system.

But the analyzed static electric field need not be generated only by a mitochondrion. Mitochondria occupy a substantial portion of the cytoplasmic volume of the eucaryotic cells. In a "standard" liver cell (hepatocyte) about 22 % of the total cell volume is occupied by mitochondria. For a spherical cell and spherical mitochondria with a radius 6 μm and 0.3 μm, respectively, the number of mitochondria per cell is $N = 1760$. The full volume of the cell is equivalent to N spherical volumes with a radius

about 0.5 μm. The average distance between mitochondria might be about 0.4 μm. Exclusion zones of different mitochondria may overlap. Overlapping may disturb water ordering. Protons may be concentrated in the boundary regions between mitochondria where the intensity of the electric field has the minimum value. Concentration profile of the proton layer and its dynamic equilibrium flow between the inner membrane and the layer remains an open question.

The cytosolic medium around mitochondria is under influence of a strong static electric field polarizing biological molecules and structures. Oscillation processes are shifted into a highly non-linear region.

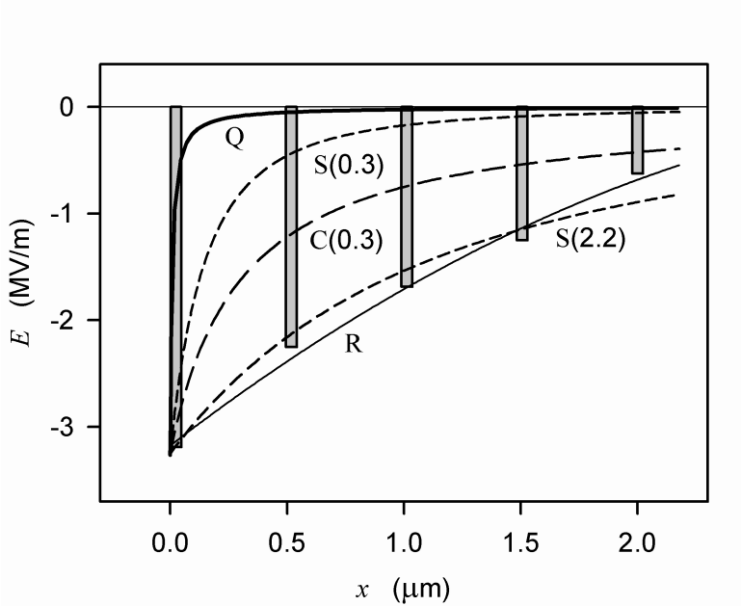


Figure 1. The intensity of the static electric field as a function of the distance from mitochondria,
Vertical bars–measured values (after Tyner et al. [59]),
R–quadratic regression curve,
S(2.2)–regression curve for spherical exclusion layer (radius of mitochondrial surface is 2.2 μm),
Q–a proton layer with no water ordering,
S(0.3) and C(0.3)–a spherical and a cylindrical exclusion layer (radius of mitochondrial surface is 0.3 μm).

Chemical energy of pyruvate and fatty acids supplied to mitochondria is used for production of ATP and GTP. The efficiency of energy conversion is of about 40 % or slightly higher. The non-utilized energy (often denoted the "wasted energy") may be nearly 60%. The non-utilized energy is liberated from mitochondria in the form of photons in the UV (Tilbury and Quickenden [60] and Batyanov [61–62]), visible, and infrared regions, heat and chemical compounds.

4. Microtubule oscillators

The cytoskeleton in eukaryotic cells is a complex network of protein filaments extending through the cytoplasm. Cytoskeleton is a dynamic structure under continuous reorganization connected with shape change, division, coordination of directed movement, organization, response to inner cellular state and environmental conditions. The filamentary structure of the cytoskeleton contains actin filaments, microtubules, intermediate filaments, and accessory proteins. Accessory proteins may have a variety of functions. Some accessory proteins may link filaments to one another. The cytoskeleton forms a compact three-dimensional network in the cytosol conditioning the cell function. Microtubules create the main structure of the network. Microtubules start to polymerize from the centrosome that is

positioned in the center of the cell. Microtubules grow in the radial direction. Some microtubules are bound to structures at the membrane. In the M phase microtubules form a mitotic spindle organized by two centrosomes (poles of the mitotic spindle). In the interphase mitochondria are aligned along microtubules. In the M phase their distribution is rather unknown. Organization of microtubules and mitochondria might be a special issue of the cellular static electric and electromagnetic field. It was observed that the microtubule structure organized by a centrosome finds the center of the cell. The cell may form an electromagnetic cavity resonator with dielectric walls (Popp [63] and Jelínek and Pokorný [64]). The position of the microtubules and the centrosome may be controlled by the cavity electromagnetic field. In the interphase organization of mitochondria depends on microtubule structure. The space distribution of the field and the acting forces are different in the interphase and in the M phase (in the one pole and the two poles structure, respectively). Mitochondria may move together with the ordered water and the proton space-charge layer. The final effect of organization may be assessed using real parameters of the system. But this problem has not been solved yet. On the other hand the static electric field might participate in mitochondrial space distribution too. Very often mitochondria remain in position where they cover unusually high ATP consumption. Due to the proton transfer and the strong static electric field mitochondria might provide a long range interactions with the "energy consumption site". The sites of increased energy consumption in the M phase have different locations in comparison with the interphase period.

Microtubule is a hollow cylindrical structure organized in protofilaments composed of tubulin heterodimers. Two globular proteins of a relative mass of about 55000 form a tubulin heterodimer. Each heterodimer is an electric dipole with a dipole moment of about 1000 Debye, i.e. 10^{-26} Cm (Satarić et al. [65] and Tuszynski et al. [66]). The induced dipole moment in a dimer generated only by the motion of mobile electrons or protons was assessed to be 200–400 Debye (Stracke et al. [67]). Polarization changes are connected with elastic oscillations.

Oscillations in microtubules require energy. Energy may be supplied by different mechanisms. Dynamic instability, motion of motor proteins, and liberation of non-utilized energy from mitochondria are the energy supplying processes. Dynamic instability is a special property of microtubules. In the interphase microtubules bound to the structures at the membrane have a turnover of about 18 hours (Pelling et al. [68]) and then they are replaced. The free end microtubules have a short turnover–about 10 min. They continuously polymerize and depolymerize. After polymerization GTP in the β tubulin is hydrolyzed to GDP. A part of the liberated energy is stored in the structure of the microtubule. In the M phase the dynamic instability has a form of treadmilling–microtubules polymerize in the central part and depolymerize at the poles of the mitotic spindle. The described mechanisms of dynamic instability supply energy to microtubules. In the M phase of the cell cycle the rate of exchange of heterodimers is more than one order of magnitude higher than in the interphase and energy supply is correspondingly increased too (Pokorný et al. [69]).

Motor proteins transport particles, vesicles, organelles, etc. along microtubules. Energy for a one "step" of a motor protein "walking" is obtained from hydrolysis of an ATP molecule. A part of the "walking" energy is transferred to microtubules. But the motor protein motion might also disturb and damp microtubule oscillations.

Non-utilized energy liberated from mitochondria may be the greatest contribution to excitation of microtubule oscillations. It may excite vibrations in a wide frequency range.

Biological electromagnetic activity–a novel issue in biology–was observed from acoustic to visible frequency range. Mechanical and electrical oscillations were measured in the acoustic range. Mechanical oscillations were disclosed by AFM (atomic force microscopy) at 1.643 and 0.87 kHz at temperature 30 and 22°C, respectively (Pelling et al. [18–19]). Mechanical and electrical oscillations in the acoustic band were measured by Jelínek et al. [20]. Frequency of oscillations was assessed from experimental result of dielectrophoretic attraction of particles in the band 5 kHz–1 MHz by Pohl [15]. Disturbances of internal cellular electromagnetic field by external electromagnetic field in the frequency range 100–300 kHz were described by Kirson et al. [21–22]. The external field disrupts polymerization of microtubules and can even destroy the cell. Electrodynamic activity of yeast cells

and alga cells was measured in the frequency range 1.5–52 MHz by Lamprecht and Hölzel [16] and Hölzel [17]. Pokorný et al. [25] observed and evaluated electrodynamic activity of yeast cells in the frequency band 8–9 MHz. The activity was measured in the M phase. The high activity coincides with the rearrangement of the microtubules into a mitotic spindle, with binding chromatids to kinetochore microtubules, and with elongation of the mitotic spindle during anaphase A and B. Resonant interaction of the electromagnetic field with a cancer tissue at 465 MHz and the first and second harmonics was disclosed by Vedruccio and Meessen [27]. Cells ability to detect electromagnetic signals of other cells in the red and near-infrared range was disclosed by Albrecht-Buehler [29–31]. The observed cells are able to sense the radiation and to determine the direction to the source.

Microtubules in vitro were measured by Sahu et al. [26] (not yet published). A novel method of polymerization was used–polymerization in the oscillating electric field. Electron conductivity in microtubules was investigated. Sahu et al. [26] claims, that electrons move along spiral orbits with different steepness of the helix with no losses (ballistic conductance). The resonant frequencies were around 10 MHz.

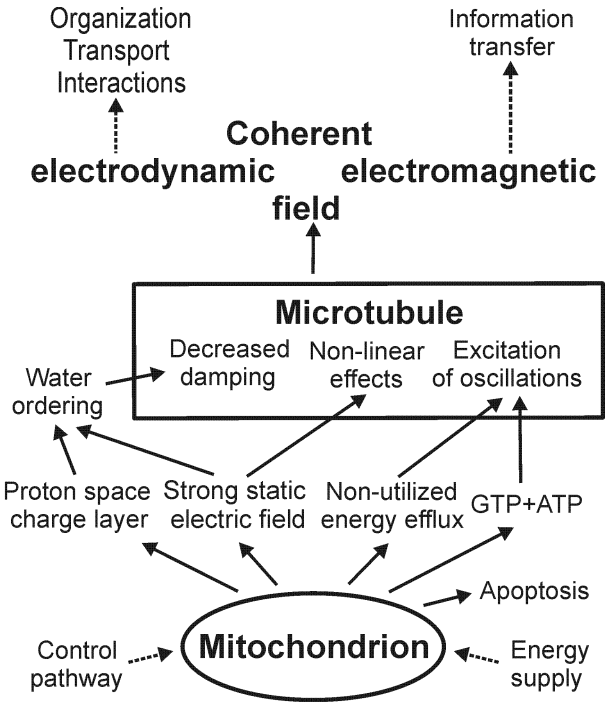


Figure 2. A schematic picture of physical mechanisms in living cells depending on mitochondrial function. Transport of protons into intermembrane space and their diffusion into the cytosol lead to formation of proton space charge layer, strong static electric field, and water ordering around mitochondria resulting in low damping of microtubule oscillations. The static electric field conditions non-linear effects in microtubule. Non-utilized energy efflux and production of ATP and GTP provide energy supply. Microtubule may generate electrodynamic ("static" and "induction"–virtual photon–field in the vicinity of the source) and electromagnetic field (radiation–photon field) at a large distance. Information may be transferred by the photon and the virtual photon field too.

The electrodynamic field measured at the membrane of living cells is assumed to be generated by fundamentally non-linear elastic-electrical oscillations of microtubules. The oscillations may display several resonant frequencies as follows from AFM measurements in the acoustic region and interaction of external electromagnetic fields with living cells, in particular in the 0.1–0.3 MHz and

465 MHz regions. A direct measurement of coherent resonant signals using special nanotechnological systems at physiological temperature may disclose essential spectral properties of oscillations in microtubules and their structures in cells.

5. Cellular physics

Cooperation of mitochondria and microtubules is a unique property in living cells and may form an essential basis for physical processes. The static electric field created by mitochondria may be a fundamental factor for establishment of non-linear properties of microtubules and ordering of water. Non-linear properties make possible special interaction between elastic and polarization fields, water is a quasi-elastic structure whose properties may be at the boundary between a liquid and a solid-state material. Non-utilized efflux of energy from mitochondria seems to be the main source for excitation of oscillation, shifting the system far from thermodynamic equilibrium, and establishment of the coherent state. A considerable part of biological activity may depend on the electrodynamic field which may play a significant role in different cellular processes. It might produce a traction force predicted by Frauenfelder et al. [70] for directed transport of material (Pokorný [71] and Pokorný et al. [35]), morphological force for organization of morphological structures, interaction force for intra and inter-cellular purposes (Pokorný [72]) and may mediate information transfer. Figure 2 shows a schematic picture of physical links of the cellular activity (Pokorný et al. [28]).

6. Physical alterations in cancer cells

Suppression of oxidative metabolism may be one of the biggest differences between healthy and cancer cells. A diverse group of signaling pathways and oncogenes may result in Warburg effect and in resistance to apoptosis. A type of Warburg effect with hyperpolarized mitochondria is in figure 3. The lack of hyperpolarization of the mitochondrial inner membrane in certain types of cancer suggests that mitochondrial dysfunction might be caused by different mechanisms.

Warburg assessed the ratio of the amount of energy produced by fermentation and oxidation (respiration) process in healthy and cancer cells. In healthy cells the oxidation energy production may be more than 10 times greater than the fermentation one (in kidney and liver cells even 100 times). With the exception of the cancer cells with reversed Warburg effect (Pavlides et al. [73]) fermentative production in cancer cells is bigger than in healthy cells. In the cancer cell fermentation may participate in energy production highly approximately by 1/3–2/3 part of the total output and the average value may be of about one half (Warburg [3–4]). If the cancer and the healthy cells have the same amount of the total energy and the same mitochondrial efficiency of utilization of the electrochemical proton gradient (by ATP synthase protein complexes) then only about one half of protons are transported across the inner membrane in comparison with a "healthy" mitochondrion.

Non-utilized energy liberated from mitochondria may be adequately lower too. The intensity of the static electric field and the level of water ordering are diminished, that have a negative impact on microtubule oscillations. Damping of oscillations is increased, excitation is lowered, and non-linear properties are shifted towards linear region. As a consequence power and coherence of the generated electrodynamic field are diminished. Coherent processes in the cell are disturbed, and randomness increased (Pokorný et al. [28,36] and Pokorný [33–34]).

Development of mitochondrial malfunction is produced before the malignant properties of cancer cells may be observed. In the cervical cells the cancer mitochondrial dysfunction turn was observed in the period precancerous–cancer cells (Jandová et al. [74]). The malignant properties, in particular local invasion and metastases, may be caused by disturbances of electromagnetic activity. Local invasion may depend on the interaction mechanisms between cells (Pokorný [72]). The interaction forces between cancer cells may be smaller than interaction forces between healthy and cancer cells. As a result cancer cells are pulled by healthy cells into healthy tissue. Disorganization of the cytoskeleton precedes the metastasis (Beil et al. 75], Suresh et al. 76], and Suresh [77]). Disturbances of the cytoskeleton together with decreased excitation and increased damping may alter the frequency spectrum and the spatial pattern of the generated electromagnetic field with such an impact that cancer

cell does not interact with the surrounding cells, can lose connection with them, can leave the tissue, move freely in the body and create a metastatic nodule even in distant organs.

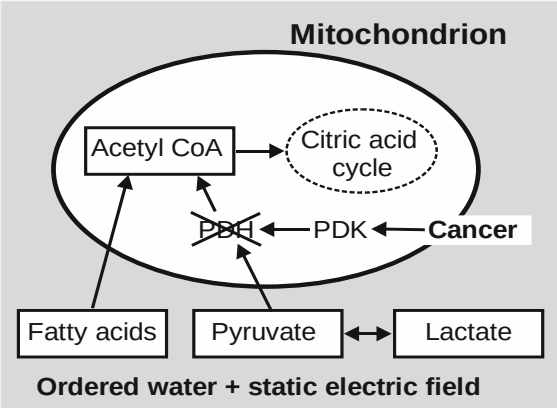


Figure 3. A schematic picture of the glycolytic phenotype of cancer cell (Bonnet et al. [83]). Cancer kinase PDK blocks the pyruvate pathway inhibiting pyruvate dehydrogenase (PDH) enzymes. Only about one half of protons are transferred across the inner membrane into intermembrane space in comparison with fully functional mitochondria. Similar effect of proton transfer inhibition may be caused by defects in the citric acid cycle.

7. Discussion

After elapse of 80 years from the discovery of the suppression of the oxidative mechanism in cancer cells, 40 years of Warburg death, and 10 years of the beginning of the endeavor to revisit the Warburg discovery, the Warburg effect has become an urgent issue. Warburg effect is now understood as one of the most important links along the cancer transformation pathway. Mitochondrial dysfunction may alter processes dependent on the energy supply, strong static electric field, and ordering of water which suggest processes of physical nature. But elucidation of such processes disturbed by the mitochondrial dysfunction is not yet performed. The consequences of the mitochondrial dysfunction may be analyzed on the basis of the Fröhlich hypothesis of electrical polar oscillations in living cells and creation of a coherent state. The Fröhlich hypothetical prediction of oscillation states was branded as impossible due to strong viscosity damping of water (Foster and Baisch [78]) or quite generally by low quality of biological oscillators (Reimers et al. [79] and McKemmish et al. [80]) neglecting interfacial and mitochondrial water ordering in cells. Reimers et al. [79] and Mc Kemmish et al. [80] analyzed linearized system neglecting essentially nonlinear interactions between elastic and polarization fields. But the Fröhlich hypothetical analysis is strongly supported by experimental findings on water ordering, static electric field created around mitochondria, and electrodynamic activity of living cells.

The directions of the future research of electromagnetic processes in living cells should be assessed. Experimental research based on nanotechnological devices makes possible in vivo and in vitro measurements of the electrodynamic field of living cells. The total turnover of the power of the cells is a basic value. Lamprecht [81] measured the yeast cell turnover to be about 10^{-13} W. A similar amount of power might excite electrodynamic oscillations in microtubules that may correspond to the non-utilized power liberated by mitochondria. Assessment of the conversion of the random supply to coherent oscillations, the number of microtubules in the cell, and the power distribution in particular frequency spectral lines, leads to conclusion that the power exciting individual microtubule spectral line may be about 10^{-17} W. The power stored in the oscillating microtubule may be of about 10^{-15} W if the quality factor is high. Measurement may strongly affect the microtubule oscillating system by increased damping and change even the frequency spectrum. In vivo measurement may be performed

at the cellular membrane at a patch corresponding to the microtubule binding spot at the inner side of the membrane (Kučera et al. [82]). The linear dimensions of the sensor for detection of the cellular signal should be smaller than about 1 μm. The physiological temperature should be maintained during measurement. Parameters of microtubules for assessment of their electrodynamics characteristic features may be determined by in vitro measurements.

Theoretical research should be bound to experimental research to solve main problems of physical processes in biological activity of living cells. Theoretical treatment should explain the main conditions for water ordering around mitochondria and its essential properties, generation of coherent electrodynamic field by microtubules, interaction inside and between cells mediated by the electrodynamic field, creation of quantum theory of coherence in biological systems, and–very likely–development of a novel fundamentally non-linear quantum (electrodynamic field) theory for biological systems.

Convergence of classical biology, molecular biology, genetics, and biochemistry with the novel biological physics is a highly important issue. The research in the future should bridge the gap between the chemical and genetic processes on the one hand and physical ones on the other hand. Conversion of both parts conditions comprehensive understanding of biological activity and cancer transformation pathway. Biochemical, genetic, and physical processes are mutually dependent and equally important. Building of more sophisticated models of biological activity is required.

A special case of theoretical and experimental investigations of physical processes in living cells concerns the cancer transformation pathway. Fundamentally disturbed electrodynamic field in cancer cells (Pokorný et al. [28,36] and Pokorný [33,34]) results from mitochondrial dysfunction caused by decreased proton pumping from the matrix space and liberation of the non-utilized energy to mitochondrial ambient medium. Mitochondrial dysfunction (that develops before appearance of the cancer malignant properties) and diminished power and coherence of the electrodynamic field may be the most pronounced differences between the healthy and the cancer cells in the clinical phase. Mitochondrial and physical processes should be targeted for cancer treatment. Cancer cell killing is the main target of the standard therapeutic strategy. Nevertheless, such treatment may also damage healthy cells and limit its further application for treatment of recurrent tumors. Restoration of normal (healthy) cell function should be–first of all–the therapeutic strategy. For instance, normal function of mitochondria is restored and the apoptotic pathway unlocked by opening the pyruvate pathway in mitochondria after inhibition of PDK. As a result, the physical processes in the cell and the cell by itself are reversed to normal operation. Consequently, the cell may trigger apoptosis after overturn from cancer to normal if the damage exceeds certain level. Targeting mitochondria acts in the region of the main differences between healthy and cancer cells.

8. Conclusions

Cooperation of mitochondria and microtubules is a unique phenomenon in living cells. Chemical and genetic signals control mitochondrial multifunctional operation. But the main part of mitochondrial activity conditions physical processes. Mitochondria transfer protons across the inner membrane, produce ATP and GTP, and release the non-utilized energy. Formation of a zone of strong static electric field in the cytosol, water ordering, and proton space charge layer are conditioned by proton pumping from the matrix space of mitochondria. The strong static electric field can shift oscillations in microtubules to highly non-linear region that makes possible creation of coherent state. Organized water form a quasi-elastic medium resulting in small damping of microtubule oscillations. A considerable part of energy supply to microtubules may be provided by liberation of non-utilized energy from mitochondria.

Electrodynamic field generated by microtubules might provide essential biological functions. Morphological organization, transport of molecules, vesicles, and reaction components, interactions inside a cell and between cells may depend on generated electrodynamic field. High capacity information transfer between the body organs and the brain may be mediated by the electromagnetic field.

Mitochondrial dysfunction in cancer cells may cause increased damping of microtubule oscillations, diminished energy supply, and shift of the non-linear properties towards linear region. Power and coherence of the cellular electrodynamic field generated in a cancer cell are diminished.

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