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Biophysical Pathology in Cancer Transformation

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Abstract

Energy supply to biological systems excites and sustains the state far from thermodynamic equilibrium which is a necessary condition for life. Energy processing by mitochondria forms a strong static electric field which causes ordering of water. These physical states establish conditions for generation of the electromagnetic field by microtubules (microtubule generation is postulated). Disturbances of the energy supply system result in pathological states. In cancers the physical pathological state is caused by disturbances of oxidative metabolism. Mitochondrial dysfunction is formed either in cancer cells (the normal Warburg effect) or in fibroblasts associated with cancer cells (the reverse Warburg effect). Dysfunctional mitochondria display inhibited pyruvate transfer into matrix space, decreased oxidative energy metabolism, low static electric field, and low level of water ordering around them. Electromagnetic fields generated by microtubules are disturbed. In the case of the normal Warburg effect electromagnetic activity of the cancer cells may be low and coherence disturbed. In the case of cancers with the reverse Warburg effect electromagnetic activity of the cancer cells may be enhanced due to fully active mitochondria and processing of energy rich metabolites supplied from associated fibroblasts. Due to nonlinear properties of microtubule oscillations the frequency spectra of the electromagnetic field generated by cancer cells may be rebuilt and shifted in comparison to standard frequency spectra of the tissue. The direction of displacement is dependent on the decreased or the increased power of oscillations. Space pattern of the field may be altered as well. Tissue interactions are changed. A cancer cell disassociates itself from interactions with healthy cells, evades the regulation and control of tissue, and may move outside its assigned position. This may constitute an essential mechanism of local invasion and metastasis. Mitochondrial dysfunction in cancers is distinct from the normal function in healthy cells and should be targeted for selective treatment.

Keywords

Cancer biophysics; Warburg effect; Reverse Warburg effect; Biological electrodynamics; Coherent states

Introduction

Biological organisms are complex systems consisting of a large number of different entities forming a nonlinear hierarchical structure. The biological complex systems interacting with surrounding medium are far from the thermodynamic equilibrium. The supply of energy and its transformation for keeping the state far from the thermodynamic equilibrium is a hallmark of life. Energy consuming mechanisms make possible targeted transport, interactions, organization, and information transfer. Any motion or action requires an energy supply and therefore, the processes involved in supplying energy belong to the essentials for biological activity. O. Warburg intuitively assessed the cancer process as a disturbance of energy transformation and utilization. He experimentally disclosed that cells from cancer tissue can approximately obtain the same amount of energy from fermentation as from respiration, whereas healthy cells obtain much more energy from oxidation than from fermentation [1,2]. Biological research orientated predominantly towards biological and genetic processes has considered the Warburg effect to be a side effect of, rather than central to the cancer process. However, positron emission tomography (PET) imaging has now confirmed that most malignant tumors have increased glucose uptake (Bonnet et al. [3]), which is consistent with the metabolic phenotype, aerobic glycolysis, described by Warburg. On the other hand, the mechanisms of the energy supply and the role of the biological electromagnetic fields cannot be understood without a deep understanding of the structure of biomolecules, chemical reactions, and genetic processes. (The electromagnetic field was experimentally proved in some biological systems and its existence in all biological systems is postulated.) Oxidative energy transformation is performed by mitochondria which are the boundary elements between chemical–genetic and physical processes [4]. The flux of electrons down the electron transport chain supplies energy for proton transport across the inner mitochondrial membrane and creation of an electrochemical potential. After diffusion through the outer membrane, protons form a charge layer around mitochondria. The negative charge in the mitochondrial matrix and the positive charge of transported protons establish a strong static electric field ordering water around mitochondria [4]. A layer consisting of a strong electric field has been measured up to a distance of about 2 μm from the surface of mitochondria [5]. In the interphase, mitochondria are aligned along microtubules and form essential conditions for generation of the electromagnetic field by microtubules (a postulate that electromagnetic field is generated by microtubules has a strong experimental support). Mitochondria supply energy, the ordered water provides low damping, and the static electric field shifts microtubule oscillations into a highly nonlinear region [4,6].

Organization of the living system depends on a supply of energy and its transformation into physical and chemical forces. A concept of physical fields in living matter was formulated by H. Fröhlich. He postulated long-range quantum mechanical phase correlations, existence of electrically polar vibration modes excited far from thermal equilibrium, and generation of endogenous coherent electromagnetic field in biological systems [7-13]. Microtubules were assumed to form the generating structures in eucaryotic cells [14-18]. Besides energy supply for excitation of oscillations mitochondria create fundamental conditions for generation of the cellular electromagnetic fields [19-21].

Fröhlich also predicted the role of endogenous polarization vibration fields in cancer development [22]. The hypothesis was based on a general assumption of interaction forces between electric vibration structures in biological systems. Cancer transformation is a multistep, multibranch, and multilevel microevolutionary process which triggers a vast spectrum of biological changes of a biochemical,

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genetic, and physical nature. The chemical and genetic changes may develop along different pathways dependent on the "type" of cancer. Warburg's discovery suggests that a large variety of biochemical–genetic pathway links join together in mitochondrial dysfunction. Bonnet et al. [3] examined the glycolytic phenotype cancer cells displaying mitochondrial dysfunction which is caused by inhibition of the pyruvate pathway into mitochondrial matrix. Cancer cells display low expression of K^+ channels in plasma membranes and inhibition of apoptosis. (Properties of the glycolytic phenotype cancers can be found in the overview by Pokorný et al. [23]). Nevertheless, not all cancers correspond to the glycolytic phenotype. Another type of energy production defects and apoptosis blocking was disclosed [24]. This type of cancer cell has high activity of mitochondria and mitochondrial dysfunction occurs in fibroblasts in the stromal microenvironment. Energy rich metabolites are transferred to cancer cells from fibroblasts associated with cancer cells (the reverse Warburg effect).

From a biophysical perspective and for development of novel methods of cancer treatment, it seems reasonable to assume that all cancers can be divided in two main groups–cancers with the normal Warburg effect and with the reverse Warburg effect. Analysis of physical properties of these two groups of cancers is a subject of this article. Individual exceptions not experimentally proved will also be discussed.

Mitochondria and microtubules

The basic processes of energy conversion are fermentation (glycolysis) and mitochondrial oxidative metabolism. Pyruvate (produced by glycolysis) and fatty acids are transported to the mitochondrial matrix, and broken down into a two-carbon acetyl group on acetyl coenzyme A (CoA). In the citric acid cycle (tricarboxylic acid cycle), the energy stored in the acetyl CoA is used for pumping protons from the matrix across the inner mitochondrial membrane and transforming it into an electrochemical proton gradient potential. The negative charge in the matrix and positive charge of protons form a strong static electric field layer around the mitochondria. The electric field has been measured up to a distance of 2 μm from the mitochondrial membrane. At the outer mitochondrial membrane the electric intensity is 3.5 MV/m [5]. Nearly linear decrease of the intensity as a function of distance is explained by water ordering [4]. A schematic picture of mitochondrial activity and its cooperation with microtubules can be seen in Figure 1.

Ordering of the cytosol water seems to be a crucial phenomenon influencing its mutually dependent elastic and electric properties, in particular damping of oscillations. Ordering is caused by the intensity of the static electric field as was studied by Ling [25]. For instance, ordered water molecules are arranged in layers equidistant from the charged planar surface. The ordered water at the interface was measured by physical methods determining its characteristic features and parameters. It has been experimentally proven that the ordered water has different physical properties compared to bulk water, including higher viscosity [26], lower thermal motion [27], different pH [28], and different spectroscopic properties [29]. Ordered water also exhibits separation of charges [28], solvent exclusion [30], and potential difference across the layer [26,27]. Ordering of water by electric fields is a general feature and may also be achieved by a static electric field of external sources. Fuchs et al. [31-33] and Giuliani et al. [34] have shown that strong electric field of about 600–700 kV/m

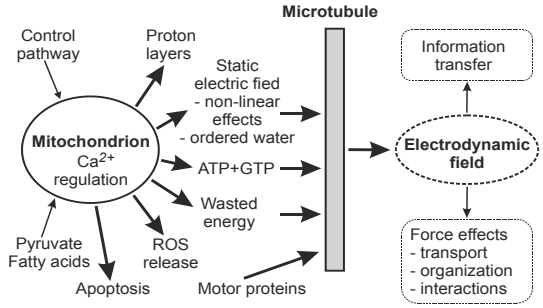


Figure 1: Physical processes in living cells. Generation of the electromagnetic field by microtubules is based on cooperation of mitochondria and microtubules. Mitochondrial transport of protons into the intermembrane space and their diffusion through the outer membrane into cytosol leads to generation of a strong static electric field. The strong static electric field causes ordering of water and shift of oscillations in microtubules into a highly nonlinear region. Energy is delivered to microtubules by hydrolysis of GTP in β tubulin after polymerization and through motion of motor proteins. Generated electrodynamic field may provide force effects in various internal processes and mediate information transfer.

organizes water and forms a floating water bridge about 1–3 cm long between two glass beakers.

Ordering of water is not only a matter of thin films of a few molecular layers. The thickness may extend to a few hundreds of micrometers. Clear water layers around microtubules have been measured by Amos [35]. Stebbings and Hunt suggested connection of clear zone formation with negative charge at the surface [36]. The clear zones around microtubules with thickness from 5 to 20 nm are now termed exclusion zones. The ions are expelled from the region of cytosolic ordered water and concentrated beyond the distant edge of the ordered region. Its outer boundary may be smeared by diffusion. Generally, water ordering is a phenomenon changing bulk water from a flowing viscous liquid into a quasi-elastic gel affecting inner cellular properties. Ordered water provides low damping of a vibration system with water surrounding, in particular of the vibrations in the cytoskeleton.

In the interphase mitochondria are aligned along microtubules, the main organizers of the cellular cytoskeleton. In the M phase distribution of mitochondria is not known. Mitochondria occupy about 22 % of the cellular volume and, therefore, the ordered water around mitochondria may fill up the rest of the volume of the cell. Low damping of the cytoskeleton vibration system conditioned by water ordering makes possible high excitation of coherent elasto-electrical oscillations [37,38]. The cytoskeleton is machinery for intracellular coordinated movements, transport of organelles, adaptation of a variety of cellular shapes, segregation of chromosomes at mitosis, reaction to surroundings, and other activities connected with the whole cell. The cytoskeleton exerts forces and generates movements without any major chemical change [39]. The cytoskeleton consists of microfilaments, intermediate filaments, microtubules and associated proteins. Microtubules form the main organizing structure of the cytoskeleton. They are composed of tubulin heterodimers, which are strong electric dipoles. Each heterodimer has a net mobile negative charge and binds 18 calcium ions. The electric dipole moment is of about 1000 Debye (10^{-26} Cm) [40,41]. Theoretical analysis of the microtubule structure disclosed their capability for mechanical elastic oscillations in the frequency range from acoustic to GHz frequency range [42-44]. In the interphase microtubules form a radial structure

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polymerizing outward from the centrosome. The centrosome is located next to the nucleus near the center of the cell. The ends of some microtubules are bound at the plasma membrane. Microtubules with a free end polymerize and depolymerize which is also connected with energy supply. In the M phase microtubules form a mitotic spindle. They polymerize at the central part of the mitotic spindle and depolymerize at the poles. The process is called treadmilling.

The nonlinearity of oscillations may depend on strong electric fields around mitochondria. Electric fields can displace charged particles from their equilibrium positions to regions of nonlinear properties. Relation between kinetic and potential energy of the oscillating particles is a subject of nonlinear laws. Nonlinear mechanisms may utilize energy from random fluctuations and vibrations and transform it into quasi coherent oscillations. There are several sources of energy supplied to microtubules. The primary supply is based on hydrolysis of GTP to GDP (guanosine triphosphate and diphosphate) in β tubulin after polymerization. Energy supply by treadmilling is more than one order of magnitude greater than that in the interphase by growth and shrinkage of microtubules [45]. Energy is also supplied by motor proteins moving along microtubules [46]. Non-utilized energy liberated from mitochondria seems to be used too. Energy from all sources is transformed into energy of the electromagnetic field.

Conditions for excitation of electrically polar oscillations in microtubules [14] and their damping [37] have been analyzed. Electric oscillations measured at the cellular membrane of living yeast cells in the M phase display enhanced electric activity in some periods coinciding with formation of the mitotic spindle and its specific developmental features [16]. Resonant frequencies of individual microtubules were measured in the frequency range from 1 kHz to 20 GHz (a schematic plot is in Figure 2 [47]). The resonant frequencies in the frequency regions of 10–30 MHz and 100–200 MHz were disclosed by measurement of DC conductivity after application of an oscillating signal and from transmittance and reflectance of microtubules without and with compensation of parasitic reactances. Resonant frequencies do not depend on the microtubule length which suggests that all heterodimers are tuned to the same frequencies in two spectral regions. The resonant peaks are not observed after release of water from the microtubule cavity.

Experimental results proved that microtubules form resonant oscillating circuits. Each heterodimer is a strong electric dipole. Due to nonlinear properties the energy of oscillations can be transformed between different frequency regions. If the energy supply is sufficiently high coherent state is formed. The water core inside the microtubule resonantly integrates all the proteins in such a way that the microtubule nanotube, irrespective of its size, functions likes a single protein. Enhanced electrodynamic activity of cells in the M phase corresponds to development of the mitotic spindle. Therefore, experimental data support the postulate that microtubules are generators of electromagnetic activity in living cells. However, direct measurement of a single microtubule in living cells seems to be beyond the present technological capabilities.

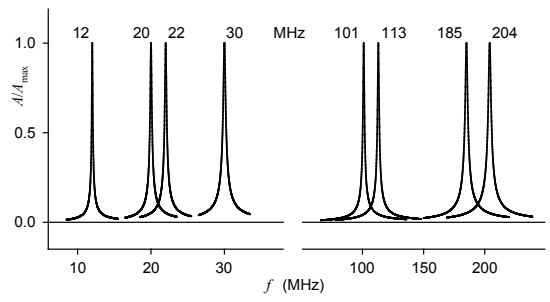


Figure 2: Resonant frequencies of the electromagnetic activity of microtubules–a schematic picture. Resonant frequencies of a single microtubule were determined by external electromagnetic signals from measurement of resistivity and transmittance and reflectance. Statistically most occurred frequencies are plotted (the real spectrum has rich bundles of spectral lines). Amplitudes of the peaks are displayed as relative values (A/A_{max}). After Sahu et al. [47].

Mitochondrial dysfunction

Otto Warburg assessed the significance of the oxidative mechanism of ATP and GTP production in mitochondria predicting that "The adenosine triphosphate synthesized by respiration therefore involves more structure than adenosine triphosphate synthesized by fermentation" [2]. Measurement of the static electric field around mitochondria [5] and its effect on water ordering support the hypothesis of the role of mitochondrial dysfunction in disturbances of biological electromagnetic fields [4].

Suppression of oxidative metabolism is a general feature of cancers and may be one of the biggest differences between healthy and cancerous tissues. Warburg assessed the ratio of the amount of energy produced by fermentation and oxidation (respiration) processes in healthy and cancer tissues. In healthy cells the oxidation energy production may be more than 10 times higher than the fermentative one (in kidney and liver cells even 100 times). Fermentative production in cancers is higher than in healthy cells and may contribute approximately by 30–70% of the total energy production output but probably averages about 50% [1,2]. If the healthy cell and the cell with dysfunctional mitochondria have the same amount of total energy for processing and the same mitochondrial efficiency of utilization of the electrochemical proton gradient (by ATP synthase protein complexes) then only about one half of protons have been transported across the inner membrane of a dysfunctional mitochondria in comparison with a fully active mitochondria. Non-utilized energy liberated from mitochondria may be correspondingly lowered too. The intensity of the static electric field and the level of water ordering are diminished creating a negative impact on microtubule oscillations. Damadian [48] explained different NMR (nuclear magnetic resonance) findings in healthy and cancer tissues by the increased freedom of motion of water molecules in cancer tissues. Damping of oscillations is increased, excitation is lowered, and nonlinear properties are shifted toward a linear region, generally resulting in decreased order. As a consequence, power and coherence of the generated electrodynamic field are diminished. Coherent processes in the cell are disturbed, and randomness increased [19-21,38].

The mechanism of disturbed oxidative mitochondrial metabolism in cancer cells caused by the normal Warburg effect was disclosed by Bonnet et al. [3]. The pyruvate dehydrogenase complex (PDH) is regulated by pyruvate dehydrogenase kinases (PDK's, isoforms PDK-1–4) and dehydrogenase phosphatases (PDP-1–2) [49]. The PDK blocks the pyruvate pathway into mitochondria. This type of mitochondrial dysfunction, termed the glycolytic phenotype, is shown in Figure 3. A result of this process is that proton transfer from the mitochondrial matrix and electrochemical potential dependent on proton transfer across the membrane are lowered. Oxidative production of ATP and GTP is diminished as a result of the pyruvate transfer inhibition caused by cancer. The cancer cells display resistance to apoptosis [3]. Different groups of pathways and oncogenes result

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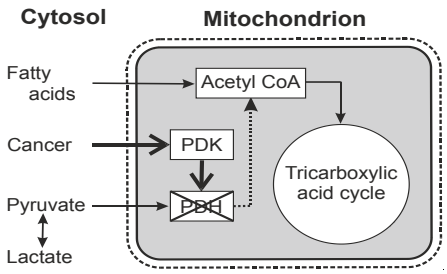


Figure 3: Mitochondrial dysfunction–inhibition of the pyruvate pathway into mitochondria. Functions of the pyruvate dehydrogenase enzymes are blocked by PDKs. Oxidative metabolism of energy production depends only on fatty acids. Fermentation may lead to production of lactic acid.

in a glycolytic phenotype and resistance to apoptosis. Mitochondrial dysfunction in cancer cells was found in many cancers [50,51], for instance, the majority of carcinomas are of glycolytic phenotype [52,53].

However, quite a different version of the cancer process was revealed by Pavlides et al. [24]. In this phenotype, the cancer cells have fully functional mitochondria but energy rich metabolites (pyruvate, lactate, glutamine etc.) produced by glycolysis are supplied from associated fibroblasts whose mitochondria are dysfunctional. Consequently, energy production and the power of the electromagnetic field in the cancer cells are high. However, microtubule oscillations may be deviated to higher nonlinear regions which can cause a shift in and rebuilding of the frequency spectrum. In this case, the supply of energy rich metabolites from the environment supports cancer cell growth and its aggressiveness. The term the 'reverse Warburg effect' has been assigned to this cancer phenotype.

Subordination of the cells in the tissue is an essential requirement for function of biological organs. Subordination based on mutual interactions between cells presumably depends on the generated electromagnetic field. Interactions between electric vibrations can provide attraction as well as repulsion forces which are results of characteristic properties of the electric vibration structures in the cells. Disturbances of its frequency spectrum would lead to local invasion and metastasis. Cancer cells may escape from interactions with the surrounding healthy cells and perform individual activity [22]. Disturbances of the space pattern of the electromagnetic field determined by geometrical arrangement of microtubules and other cytoskeleton structures may produce a similar effect. Disorganization of the cytoskeleton precedes metastasis [54]. An example of this could be the epithelial–mesenchymal transition where epithelial cells lose their polarity as well as their adhesion to other cells and begin to migrate invasively

Membrane potential of mitochondria

Functional mitochondria build a negative-inside potential across the inner membrane which is dependent on the distribution of the negative and positive charges connected with mitochondrial function–transfer of positively charged protons across the inner membrane [55]. The fluorescent method of measurement of the membrane potential is based on uptake and retention of positively charged fluorescent dyes (URFD). Molecules of the dyes are attracted by the matrix negative charge and replace protons in their positions (nevertheless, URFD depends not only on the mitochondrial membrane potential but also on the distribution of ions in the cell). A large number of fluorescent dyes have convenient properties for measurement of the membrane potential. One of the highly specific dyes for this purpose is Rhodamine 123 (Rh123) with a delocalized positive charge [52,56]. Dependence of URFD (examined by Rh123) on the negative potential was measured on isolated mitochondria [57]. The level of absorbance and fluorescence values is a function of the membrane potential [52]. The fluorescence is a linear function of the membrane potential from the absolute value of about 60 mV.

The fluorescent dye measurement method has been used for assessment of mitochondrial potential differences between healthy and cancerous cells. Mitochondria in normal healthy cells display low URFD [52,58]. In contrast a great majority of adenocarcinoma, transitional cell carcinoma, squamous cell carcinoma, and melanoma have high URFD [52,59]. A profound relationship between differences in URFD and tumorigenic properties was found, which are described below. The URFD makes possible determination of the probability of colonic tumor expansion and progression [60,61].

The URFD value in cancer cells MIP101 and CX-1 (both human colon carcinomas) are higher than the URFD of healthy cells CV-1 (monkey kidney epithelial cells) [57]. The difference corresponds to about 60 mV. Increased URFD examined by the tetramethyl rhodamine methyl ester (TMRM) was observed on several types of cancer cells with inhibited pyruvate transfer into mitochondria [3]. Restoration of pyruvate transfer by application of dichloroacetate (DCA) results in increased oxidative mitochondrial activity, reversal of URFD from high to low value, and bringing back parameters of healthy cells. Similar results were measured by protonophore (carbonylcyanide-p-trifluoromethoxyphenylhydrazone, FCCP). The high URFD was measured on cells with inhibited pyruvate transfer in mitochondria and suppressed oxidative metabolism.

Examination of different cancer cells revealed different URFD by mitochondria before and after cancer transformation. Two opposite cases were measured. For instance, v-fos oncogene transformed fibroblasts have been shown to have higher URFD in comparison with their untransformed counterparts [62]. In contrast, v-fes oncogene transformed mink fibroblasts display change from a state of high URFD and low pH gradient to a state of very low URFD and very high pH gradient [52,63]. Mitochondria in two human colon carcinoma cell lines had URFD lower than their healthy counterparts and nigericin failed to hyperpolarize the mitochondria [64].

The measured data demonstrate two types of cancers–one with high and one with low URFD. The URFD in glycolytic phenotype cancer cells is high. On the other hand, both the healthy cells and the cancer cells in cancers with the reverse Warburg effect have high oxidative metabolism with high transfer of protons from the matrix. The URFD in these cancer cells is low. However, the URFD does not depend only on the membrane potential created by proton transfer and may be affected by other parameters such as cell growth [52,65], the plasma membrane potential, distribution of ions such as K^+ and ionophores [66], distribution of charged molecules such as lactate, and ordered water layer around mitochondria. Apart from all mentioned agents and influences, during continuous respiration some compounds such as nigericin hyperpolarize mitochondria by electrically neutral exchange of protons for K^+ ions leading to decrease of the pH gradient and an increase of the membrane potential in compensation for the change of electrochemical potential [63,66]. In the published papers the low and the high URFD values have

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been assigned to the low and the high negative membrane potential, respectively. The high URFD value is termed hyperpolarization. The URFD measurement can distinguish cells with the normal and the reverse Warburg effect.

Basic processes of life may be affected by mitochondrial dysfunction caused generally by disturbances or insufficient energy supply of pyruvate or fatty acids. Defects of energy processing and supply may be a general feature of many different pathological states. The pathological state need not depend on the decrease of the amount of ATP or GTP produced by oxidative metabolism but on changed conditions in the cell caused by mitochondrial dysfunction.

Some Features of Cancers with the Reverse Warburg Effect

Cancer cell effects on stroma have also been observed and suggested as a separate mechanism of response of myofibroblasts to invasive neoplasia [67]. It is also believed that both the malignant tumor cells and the surrounding or adjacent normal area have undergone a mysterious "cancerization" process as was mentioned by Martinez-Outschoorn et al. [68]. Pavlides et al. [24,69,70] disclosed that some cancer cells have fully functional mitochondria and a supply of products of aerobic glycolysis from their surroundings. The oxidative energy production may be greater than in healthy cells. Tumor–stroma co-evolution is also described [71]. The reverse Warburg effect has been observed in breast cancers, advanced prostatic cancers, and very likely may exist in many different types of epithelial cancers dependent on tumor microenvironment [24,68,69,72,73]. One of the essential conditions for creation of the reverse Warburg effect is a loss of stromal Caveolin-1 (Cav-1) expression [24,69,73-76] which induces oxidative stress driving autophagy/mitophagy [69,76,77].

Tumor growth and metastasis are fueled by a supply of energy rich metabolites, such as lactate, pyruvate, glutamine, keton BHB (beta-hydroxybutyrate) from associated fibroblasts [24,69,72,75,78]. The supply of energy rich metabolites [77], loss of Cav-1 in stromal fibroblasts [68], and their oxidative stress drive the onset of an anti-oxidant defense in cancer cells protecting them against apoptosis [71].

The mechanism of fibroblast degradation for production and secretion of energy rich metabolites depends on ROS production by the cancer cell. Cav-1 is an inhibitor of nitric oxide (NO) production in fibroblasts. A loss of Cav-1 causes increased NO production, which leads to mitochondrial dysfunction, increased ROS production, and enlarged oxidative stress [68,71].

Physical links to malignancy

Cancer growth is connected with typical features and patterns. One of the general features is proliferation. The initial noninvasive local growth of cancer often forms a structure that lacks the typical pattern of the corresponding normal tissue–very often a disorganized cell arrangement. Local invasion is a mechanism of the movement of cancer cells inside their immediate surroundings, which is assumed to be a result of active locomotion rather than passive transport caused by pressure. Displacement of a cancer cell from its original position and its migration to other tissues and organs in the body is a beginning of metastasis. Even a single cell can adhere and promote a secondary tumor. Local invasion and metastasis belong to the malignant links of the cancer process.

Two basic types of cancers have been proposed–cancers with mitochondrial dysfunction in cancer cells or in fibroblasts associated with cancer cells; URFD's by mitochondria in cancer cells is high (hyperpolarization) or low (low polarization such as in healthy cells), respectively. The cancer cells with mitochondrial dysfunction have lower biological activity than healthy cells. The cancer cells with fully functional mitochondria and a supply of energy rich metabolites display higher biological activity than healthy cells and high aggressiveness. Effects of mitochondrial dysfunction and mitochondrial high function on biological activity of cancer cells are assessed on the basis of electromagnetic fields generated by electric vibrations in microtubules (generation by microtubules is postulated). The power of their generated electromagnetic fields is diminished and coherence disturbed in the case of the normal Warburg effect (Table 1). Mitochondrial energy production and the power of the electromagnetic fields generated by microtubules are high in the case of the reverse Warburg effect. Due to the nonlinearity of oscillations in microtubules electromagnetic fields generated by both types of cancer cells differ from the field of a healthy cell. Frequency spectra of the fields are rebuilt and shifted into the frequency ranges outside the range of healthy cells. The frequency shifts depend on the power of oscillations and character of nonlinear properties of microtubules.

Together, these biophysical data support the concept that mutual interactions between cells, as well as cell control and regulation in tissue, depend not only on chemical bonds but also on endogenously generated elastic and electromagnetic fields, specifically their power, frequency spectra, and spatial patterns. Cancer cells can escape from tissue regulation and embark on unregulated, individual activity if the frequency spectra (and also spatial patterns) of their electric vibration

Table 1: Energy stored in cellular microtubule structure (E_m), power of microtubule oscillations which may be used for work (P_E), and power lost by damping caused by ambient medium of microtubules (P_L).

		Healthy	Cancer (normal Warburg effect)		
Q		100	5	3	2
E_m	(J) $x10^{21}$	16	0.8	0.48	0.32
P_E	(W) $x10^{14}$	0.98	0.6	0.33	0
P_L	(W) $x10^{14}$	0.02	0.4	0.66	1.0

Q is quality factor of microtubule oscillators dependent on damping, excitation power is 0.01 pW, and frequency 10 MHz. Energy of oscillations for Q = 2 is assumed to be too small for utilization in biological processes. In cancer cells with the reverse Warburg effect the excitation power is higher than 0.01 pW. In cancers with the normal Warburg effect the high damping of microtubules causes low energy transferred through oscillations for biological purposes.

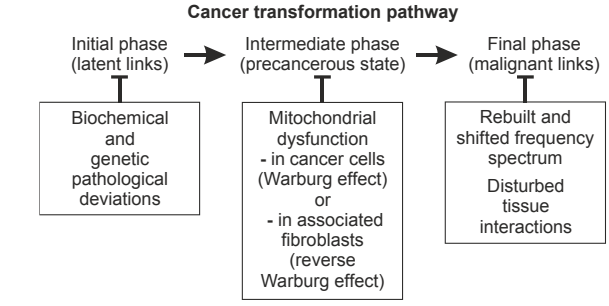


Figure 4: Cancer transformation pathway including mitochondrial dysfunction. In general, three main functional links may exist: Chemical–genetic links represent the initial phase, formation of the normal or the reverse Warburg effect the intermediate phase, and rebuilt and shifted frequency spectrum resulting in escape of cancer cells from the tissue control the final hypothetical phase [86].

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fields are different from those of healthy cells (as was suggested by Fröhlich [22]) because the tissue control and regulation of the deviated cell is diminished or completely ineffective. Thus, in both cases of the Warburg effect the cancer cells can escape from the control of the surrounding tissue and begin independent activity. Figure 4 shows the cancer transformation pathway (with a hypothetical term of disturbed electromagnetic fields) for both Warburg phenotypes–mitochondrial dysfunction in the cancer cell and in the associated fibroblasts.

The position of the Warburg effect links along the cancer transformation pathway is essential for analysis of their biological significance. For this purpose the response of the cell mediated immunity to the LDH virus antigen was investigated. T lymphocytes were prepared from venous blood of healthy women, patients with cervical precancerous lesions and cervical cancer. LDH virus antigen was prepared from the serum of inbred mice of C3H H^{2k} strain infected with the LDH virus that produces LDH isoenzymes. Effect of LDH virus antigen suggests that cervical cancer transformation connected with reduction of mitochondrial activity may yield similar results as processes in LDH virus infection. Therefore, in cervical cancer development the glycolytic and the mitochondrial oxidative energy production may be transformed in the precancerous link of cancer transformation, which is the last step before local invasion and metastasis [79]. Experimental results measured with LDH virus antigen support the hypothetical position of the mitochondrial dysfunction link along the cancer transformation pathway in Figure 4.

The vast majority of cancers are of normal and reverse Warburg effect phenotypes. Therefore, the rich variety of biochemical–genetic links has to narrow to a transition across the mitochondrial dysfunction link which cannot be bypassed. A rare specimen might be the cancer initiated by asbestos as is analyzed in Discussion.

Rebuilt and shifted frequency spectra (Figure 5) and disturbed spatial patterns of the electromagnetic fields in cancer cells in both Warburg phenotypes establish conditions for local invasion and metastasis. A schematic hypothetical picture of the level of electromagnetic activity as a function of frequency generated by healthy and cancer cells is in Figure 6. An example of a frequency shift is given. Absorption resonance frequency of cancer tissues was found by Vedruccio at about 465 MHz [38]. The force constant in the potential valley of the electromagnetic oscillators in microtubules is assumed to decrease with increasing excitation (which is a standard characteristic of one type of nonlinear oscillators). For cancers of the glycolytic phenotype the frequency 465 MHz corresponds to displaced spectral lines of healthy cells in the frequency band below 200 MHz. Nanotechnological measurement of cellular electromagnetic activity will portray the whole process.

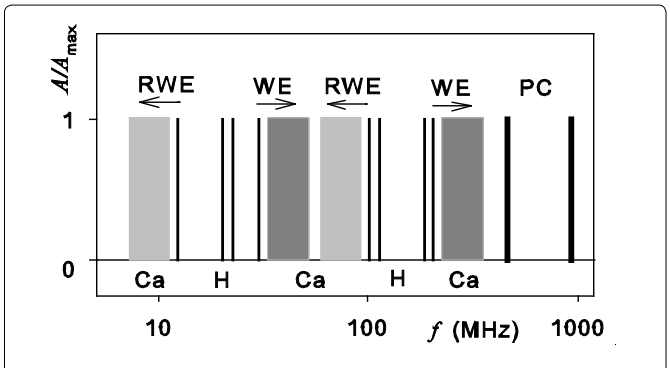


Figure 5: Hypothesis of frequency shifts of oscillations in microtubules in cancer cells (a schematic picture). The steepness of the potential valley of microtubule oscillators is assumed to decrease with increasing potential. Resonant frequencies of oscillations in microtubules in healthy cells (H) in the frequency range 10–30 and 100–200 MHz (plotted by vertical solid lines) are assumed to be shifted to higher or to lower frequencies in cancer cells (Ca) with the normal (the dark grey regions) and the reverse Warburg effect (the light grey regions), respectively. The measured absorption frequency of prostate cancer and its first harmonics (PC) are plotted in thick solid lines. The arrows denote directions of the frequency shifts caused by cancer.

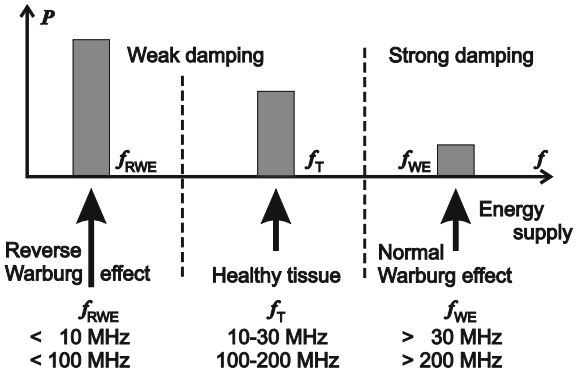


Figure 6: Hypothesis of physical basis of malignity. A schematic picture of the power spectrum (*P*) of the electromagnetic field generated by microtubules versus frequency (*f*). Frequency spectra of cancer cells with the normal and the reverse Warburg effects are shifted in opposite directions with respect to a spectrum of a healthy cell. Cancer cells with the normal and the reverse Warburg effects generate electromagnetic field with lower and higher power than healthy cells, due to strong damping and high energy supply, respectively. f_T, f_{WE}, and f_{RWE} are frequencies of microtubule oscillations in a healthy cell and cancer cells with the normal and the reverse Warburg effects, respectively. Arrows denote energy supply to microtubule.

Discussion

The normal and the reverse Warburg effects represent a key link in cancer transformation. Both types of the Warburg effect very likely form a link along the transformation pathway as a result of biochemical–genetic defects before appearance of malignity. Regardless of the fact that electromagnetic activity was measured in many biological cells, properties of individual microtubules were experimentally mapped in detail, and generation by microtubules seems to be a natural process, the electromagnetic activity of cells and its microtubule source have to be considered as postulated. Extensive experimental studies will bring necessary foundation of a novel biological discipline.

Measurement of the mitochondrial inner membrane potential makes it possible to distinguish between the two types of cancer cells. URFD is high in cancer cells with dysfunctional mitochondria and low in healthy cells and cancer cells with fully functional mitochondria. Therefore, there is a contradiction between URFD data and the real membrane potential formed by the transfer of protons. Modica-Napolitano and Aprille [57] determined the membrane potential difference in healthy cells (isolated rat liver mitochondria–CU-1) of about 104 mV and in cancer cells (CX-1) of about 163 mV. The high value of URFD in cancer cells corresponds to inhibition of pyruvate transfer into matrix and to production of lactate. However, the experimental data from the URFD measurement of the potential across the inner membrane was interpreted without analysis of possible physical mechanisms that might disturb conditions during measurement. One of them is the ordered water layer around

mitochondria. If the membrane potential is low and the intensity of the electric field cannot provide significant water ordering then all transferred protons may be concentrated in a layer at the membrane. For higher membrane potential an ordered layer of water is built. Special conditions may be formed. The protons might be distributed in two layers–an inner layer at the membrane and another at the outer rim of the ordered layer of water. In this case it is very likely that only a part of the membrane potential forming the layer at the outer rim is measured by URFD. Nevertheless, distribution of positive and negative ions in the cell (for instance, K^+ ions at the plasma membrane) may affect the measured URFD too. Lactate production is increased in connection with inhibition of pyruvate transfer into the matrix and lactate dehydrogenase reactions. Production of negatively charged lactates might in a final effect result in an increased number of hydrogen ions to maintain electroneutrality.

Lactate can be produced from pyruvate via the enzyme lactate dehydrogenase (LDH). Large activity of LDH (now classified as NAD 1.1.1.27 Oxidoreductase) enzymes is manifested in plasma during infection by lactate dehydrogenase elevating virus (LDV). LDV establishes lifelong persistent viremia in mice, parasites on energy system, and is observed as a dark particle at mitochondria [79]. Possible role of LDV in cancer origin, course, and progress is not clear.

One hypothesis claims that mitochondrial dysfunction may be a primary cause of cancer and that biochemical and genetic deviations develop as a consequent event [80]. Such a hypothesis is in contradiction with experimental result that mitochondrial dysfunction is formed in the link of precancerous cervical lesions caused by previous changes [79]. However, in special cases dysfunction of mitochondria might be directly caused by a specific agent with no previous alterations of chemical and genetic processes.

Generation of the cellular electromagnetic field may also be disturbed by conductivity changes in the cell. Asbestos may form optical fibers for cellular fields [81]. Apart from that, specific proteins and molecules containing iron atoms may be absorbed at its surface forming a conductive layer [82]. Asbestos short-circuits distant parts inside the cell with different levels of the electromagnetic field. Nevertheless, other hypotheses explain asbestos carcinogenicity on the basis of the mechanism of oxidative stress and chromosome tangling [82].

Conventional strategy of cancer treatment is directed to killing cancer cells. However, healthy cells are also impaired which limits the treatment. The treatment is aimed to destruction of the cellular nucleus which is based on the present knowledge of chemical–genetic defects caused by cancer development. Cancer research is oriented to improve killing cancer cells and to diminish undesirable defects of healthy cells, in particular by selective targeting only cancer cells (nevertheless, not realized up to now). A novel perspective strategy should be directed to the central point of cancer, i.e. to the mitochondrial dysfunction. Restoration of normal mitochondrial function and normal healthy state of cancer cell would open an effective method to fight cancer.

Cancers of different origins related to genetic and biochemical disturbances develop to a point where mitochondrial dysfunction is created. Mitochondrial dysfunction is followed by local invasion and metastasis. There are only two types of mitochondrial dysfunction and, therefore, they form a narrow neck of the transformation pathway that cannot be bypassed. The normal and the reverse Warburg effects may be the turning points in the vast majority of cancers for creating local invasion and metastasis. Different types of tumors can be vulnerable at this link and might be destroyed by restoration of normal mitochondrial function in cancer cells and/or their associated fibroblasts. In the glycolytic phenotype cancers mitochondrial dysfunction is caused by inhibition of pyruvate transfer by a kinase produced by cancer process. Generally, mitochondrial dysfunction is a final effect of genetic changes in cellular and mitochondrial DNA, epigenetic changes, malfunction of genomic processes, and biochemical disturbances. Studies of these pathways to mitochondrial dysfunction can establish novel groundwork for treatment. A variety of factors such as oncogenic signals and mtDNA mutations are mentioned as the cause of mitochondrial dysfunction [83]. However, description of the particular mechanism of mitochondrial dysfunction remains on the level of PDK's published in [3]. Overview of biochemical mechanisms promoting and inhibiting mitochondrial function and drugs which intervene in them may be important for targeted treatment.

Activity of biological cells are described in terms of chemical signaling, information transfer from genes for production of proteins, and other mechanistic activities under general control executed by the tissue, brain, and the remaining parts of the body. The cell should be an obedient machine. But cancer cells perform independent activity that is different from healthy cells (for example the epithelial–mesenchymal transition). A program of cellular activity might be an issue of evolution, development, and storage in memory. Mechanisms might depend on microtubules which are engaged in a number of cellular activities. A single microtubule has about 500 bits of memory capacity as described by Sahu et al. [84]. The total digital microtubule memory in a cell can have the capacity of about 20 kB. Microtubules also behave as bimolecular transistors capable of amplifying electric signals [85] and performing information processing. The cell might have a control and decision system. It might be assumed that DNA represents a read only memory (ROM) for material building of the cell while microtubules constitute a random access memory (RAM) and a processing unit. This elementary biological computing system could be important in cellular activity and in malignant behavior too.

Conclusion

Energy supply and its transformation into a convenient form is a necessary condition for life. The activity of a living system depends on promotion of a coherent state far from thermodynamic equilibrium. Disturbances of energy processing systems lead to disturbances of healthy activity and establishment of a pathological state. Defects in energy processing leading to decrease of the level of the excited coherent state may be latent for a long period before malignancy manifests.

Cancer develops from crucial deviations of epigenetic, biochemical and genetic nature. The decisive link to set up malignancy along the cancer transformation pathway is the transfer of biochemical–genetic disturbances to the energy processing system. Cancer therefore attacks the background of life, i.e. the coherent state far from thermodynamic equilibrium. Generally, there are two types of disturbances: dysfunction of mitochondria in cancer cells (the normal Warburg effect) and in fibroblasts associated with cancer cells that have fully active mitochondria (the reverse Warburg effect). Conditions for generation of the electrodynamic field are altered. In a cancer cell with the normal Warburg effect the static electric field around mitochondria may be low, accompanied by decreased water ordering level, high damping of microtubule oscillations, low

electromagnetic activity, and decreases in coherence. In cancers with the reverse Warburg effect the energy rich metabolites from associated fibroblasts with dysfunctional mitochondria are supplied to cancer cells whose electromagnetic activity may be strongly enhanced. In both cases due to nonlinear conditions in microtubules, the generated frequency spectra of the electromagnetic fields are rebuilt and shifted outside the healthy tissue region. Interactions between cancer cells and normal tissue cells are defective. A cancer cell may start its individual activity independent of the tissue. Malignancy is promoted by mitochondrial dysfunction. The main strategy of treatment should be targeted to restoration of a normal mitochondrial function and coherent states in deviated cells. Killing pathological cells should represent only an auxiliary method. For further understanding of the cancer process, nanotechnological measurement of the electromagnetic activity of cells is necessary to disclose the main features of pathological disturbances of coherent states.

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