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CANCER — PATHOLOGICAL BREAKDOWN OF COHERENT ENERGY STATES

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The fundamental property of biological systems is a coherent state far from thermodynamic equilibrium excited and sustained by energy supply. Mitochondria in eukaryotic cells produce energy and form conditions for excitation of oscillations in microtubules. Microtubule polar oscillations generate a coherent state far from thermodynamic equilibrium which makes possible cooperation of cells in the tissue. Mitochondrial dysfunction (the Warburg effect) in cancer development breaks down energy of the coherent state far from thermodynamic equilibrium and excludes the afflicted cell from the ordered multicellular tissue system. Cancer lowering of energy and coherence of the state far from thermodynamic equilibrium is the biggest difference from the healthy cells. Cancer treatment should target mitochondrial dysfunction to restore the coherent state far from thermodynamic equilibrium, apoptotic pathway, and subordination of the cell in the tissue. A vast variety of genetic changes and other disturbances in different cancers can result in several triggers of mitochondrial dysfunction. In cancers with the Warburg effect, mitochondrial dysfunction can be treated by inhibition of four isoforms of pyruvate dehydrogenase kinases. Treatment of the reverse Warburg effect cancers would be more complicated. Disturbances of cellular electromagnetic activity by conducting and asbestos fibers present a special problem of treatment.

Keywords: Cancer electrodynamics; breakdown of coherent states; Warburg effect.

1. Introduction

Biological systems are complex structures organized from elementary mass units containing individual parts at different hierarchical levels. Properties of the parts and of the whole system are created by the structural organization. A mammalian body is arranged from elementary living units — cells created during embryo development after fertilization of the egg. The fertilized egg cleaves and forms many small cells, then a basic body plan is created, the rudiments of organs set up, and tiny organs to the adult shape formed. All cells and their subunits are built from atoms and molecules which are not living forms themselves. The living state is established in the composed system. After inclusion of new macromolecules and particles into the cell they become a part of the living system. Transformation of the composed structures into living state is an essential question. The mature egg in a mammalian ovary is a living system. Physical processes could establish life in structures created on the basis of chemical reactions and chemical binding. It is known that energy is continuously supplied to any biological system. Any component of the biological activity (for instance transport, organization, motion, brain activity etc.) depends on energy supply. Energy transformation processes and energy excitations are inseparable parts of living systems. The energy supply creates and sustains a state far from the thermodynamic equilibrium which is considered to be the basis of life. Formation of this state is conditioned by low energy losses by damping, emission, and parasitic consumption. The state far from the thermodynamic equilibrium very likely impresses a pattern of non-random coherent activity correlated in space

and time in the biological system. As the pattern of correlation and coherence is expressed in the whole biological system regardless of its dimensions, a long-range mechanism based on physical forces is assumed. Due to an exceptional electric polarity of components and structures of living cells, the acting forces are assumed to be of electrodynamic and electromagnetic origin. The generation processes seem to depend on frequency region. Nonlinear interaction between elastic and polarization fields with random excitations could generate electrodynamic activity in low frequency bands (these processes could be combined with free charge oscillations). Photons released from chemical reaction are important for excitation in UV and visible range. Electrodynamic activity is a fundamental property of biological systems performing energy transformation for mechanical work and information transfer.

Biological systems are dependent on the ambient medium. They interact with the surroundings, uptake mass, energy, and obtain information from it. Each biological system detects its difference from the surroundings based at least on sensing random or unfamiliar coherent signals. Biological systems evaluate their difference from the medium around them. There are further properties of living entities. Even very simple systems like viruses strive for continuation in time of their own entity and/or their descendants. Biological systems endeavor to provide the most convenient conditions for their existence to avoid disturbances endangering their normal state or their existence. Pathological states may be caused by disturbances of any part and/or activity of the complex system, in particular of material, organization, and the state far from the thermodynamic equilibrium. Diseases based on pathological defects of cellular energy systems were experimentally studied by Jandová *et al.*[1]

It is well known that the majority of proteins and protein structures are electrically polar. They are electric dipoles or multipoles and any vibration generates electromagnetic field. Consequently, the biological activity should depend not only on the biochemical–genetic processes but also on the biophysical mechanisms with the dominant role of the electromagnetic field. Research on the electromagnetic activity of biological systems was initiated by H. Fröhlich at the first Versailles conference on Theoretical Physics and Biology in 1967.[2] Fröhlich formulated a hypothesis of a strong excitation of one or a few modes of motion, stabilized due to low emission and friction losses, phase correlated over macroscopic regions, and superimposed on random thermal fluctuations. The strong electric polarity of biological objects suggested longitudinal electric oscillations as stabilizing modes. Taking into account the physical principles of the electrodynamic activity, Fröhlich[3–6] formulated possible mechanisms based on nonlinear interactions between longitudinal elastic and electric polarization fields, energy transfer between normal modes along frequency scale, and energy condensation in the lowest frequency mode.

Fröhlich's hypothesis laid the basis for understanding physical processes in biological systems. Fröhlich also assumed that the cancer transformation pathway includes a link with altered coherent electric vibrations. A cancer cell may escape

from interactions with the surrounding healthy cells and may perform individual independent activity if the frequency spectrum is rebuilt and shifted.[7] The frequency changes may be combined with disturbances of the spatial pattern of the field. The transformed cell is released from local interactions and prepared to undergo local invasion and formation of metastases. Fröhlich was ahead of his time. Biological research at that period was orientated towards the chemical reaction and the genetic code problems and the Fröhlich's hypothesis was not considered to have any biological significance.

Fröhlich's hypothesis of polar modes, generation of the electromagnetic field, and its role in biological activity and the cancer transformation is a logical continuation of Warburg's discovery of partial suppression of the oxidative metabolism in cancer tissues. O. Warburg intuitively assessed the cancer transformation as a disturbance of the energy processing system. He experimentally proved that cells from a cancer tissue can obtain approximately the same amount of energy from fermentation as from oxidation, whereas healthy cells obtain much more energy from oxidation than from fermentation.[8,9] In the time of Warburg's life the defect of oxidative metabolism was considered to be a side effect, rather than the main point of the cancer process. Most malignant tumors have an increased glucose uptake as was disclosed by positron emission tomography (PET) imaging and published by Bonnet *et al.*,[10] which is consistent with the metabolic phenotype of the aerobic glycolysis described by Warburg. The decreased oxidative metabolism is caused by dysfunction of mitochondria in cancer cells. Recently, a modified version of the Warburg effect was revealed by Pavlides *et al.*[11] The cancer cell (for instance, an epithelial breast cancer cell) has a fully functional mitochondria and the mitochondrial dysfunction is transferred to fibroblasts associated with the cancer cell. Fibroblasts supply energy rich metabolites to the cancer cell. This type of cancer is connected with the term the reverse Warburg effect.

Mitochondria form a boundary between biochemical–genetic and physical processes of energy transformation and utilization. Chemical signals switch the function of pyruvate dehydrogenase complex on and off and in this way regulate the mitochondrial function and the physical processes dependent on energy supply. The role of mitochondrial dysfunction in cancer development is central for the creation of malignancy. In a cervical cancer the mitochondrial dysfunction is formed in the transformation link from precancerous to cancer cells as was experimentally studied by Jandová *et al.*[12] Therefore, in cervical cancers local invasion and the process of metastases develop after establishment of the mitochondrial dysfunction. Degradation of the mitochondrial function is at the beginning of cancer generalization.

This paper analyses and describes the role of mitochondria in generation of the polar oscillations in microtubules, their role in biological activity, excitation and maintenance of the coherent state far from the thermodynamic equilibrium. Studies of cancer disturbances of the coherent state far from the thermodynamic equilibrium as a central cancer problem are included.

2. Electromagnetic Activity of Living Cells

Electric and electromagnetic oscillations have been measured on living cells. Pohl, Pohl *et al.*, and Roy *et al.*[13–15] observed attraction of small dielectric particles to living cells and assessed the corresponding frequency of oscillations in the range below 10 MHz. Pohl explained the observed phenomenon by dielectrophoresis.[16] The greater the permittivity of the particles and the smaller the conductivity of the cellular suspension, the greater the number of attracted particles. Beside dielectrophoretic measurements of yeast and alga cells, Hölzel and Lamprecht and Hölzel[17,18] also measured oscillations in the frequency range 1.5–52 MHz using a special detection and amplification system. Electric oscillations of yeast cells in the range 8–9 MHz were measured by Pokorný *et al.*[19] Mechanical vibrations of the membranes of yeast cells in the acoustic frequency region were measured by Pelling *et al.*[20,21] by AFM (Atomic Force Microscope). The mechanical vibrations measured by AFM were compared with the electric oscillations detected at the yeast cell membranes.[22] Damping of the external electromagnetic field by the cancer tissue at the frequency 465 MHz and its first harmonic was measured by Vedruccio and Meessen.[23] Electromagnetic field generated by living cells in the red and near-infrared region and causing interaction between them was measured by Albrecht-Buehler.[24–26] Cells also detect electromagnetic signals and send pseudopodia to the source. The photon emission from living bodies was measured for instance by Popp.[27] The experimental results suggest that eucaryotic living cells can generate electromagnetic field in a wide frequency region.

3. Oscillations in Microtubules

Microtubules form a part of a well-organized cytoskeleton structure. Cytoskeleton is a specific filamentous network in eucaryotic cells exerting forces and generating movements without any major chemical change. Eucaryotic cells can form multicellular structures and systems. Eucaryotic cell's capability to create multicellular organisms depends on communication and cohesion between the cells.

The structures generating the electromagnetic field have to be electrically polar, nonlinear, and excited by energy supply. Analyses of properties of such cellular structures were published after Fröhlich's death. Fröhlich[6] assumed generation by the plasma membrane. Microtubule filaments — hollow tubes with the inner and outer diameter 17 and 25 nm, respectively — were described by Amos and Klug.[28] Microtubules grow from the centrosome in the center of the cell and form a radial cellular structure which is the main organizer of the cytoskeleton. Large dielectrophoretic effects of the yeast cells in the M phase (when cells divide and the microtubule activity is high) were measured by Pohl *et al.*[14] Tuszyński *et al.*[29] proved that heterodimers in microtubules are electric dipoles. Generation of the electromagnetic field by microtubules based on Fröhlich's mechanism of the electrical polar vibrations was proposed by Pokorný *et al.*[30] Electric oscillations measured at the cellular membrane of living yeast cells in the M phase display enhanced electric activity in

some periods coinciding with mitotic spindle formation, metaphase, and anaphase A and B.[19] Disruption of microtubule polymerization in cells by an external electromagnetic field at the frequency 0.1–0.3 MHz suggests microtubule electromagnetic activity in heterodimer attachment.[31]

Resonant frequencies of microtubules were measured in the frequency range of 10–30 MHz and 100–200 MHz by Sahu *et al.*[32] The resonant frequencies were disclosed by measurement of DC conductivity after application of the oscillating electromagnetic signal and from transmittance and reflectance of microtubules without and with a compensation of parasitic reactances in the frequency range of 1 kHz–1.3 GHz. The resonant frequencies do not depend on the length of the microtubule. After release of water from the microtubule cavity, the peaks of resonance are not observed.

The experimental results proved that microtubules form resonant oscillating circuits. Nonlinear properties of microtubules make possible transformation of the energy of oscillations between different frequency regions. If the energy supply is sufficiently high a coherent state may be formed. The water core inside the microtubule resonantly integrates all the heterodimers in such a way that the microtubule nanotube functions like a single heterodimer irrespective of the microtubule size. The enhanced electrodynamic activity of the cells in the M phase corresponds to the development and functions of the mitotic spindle. Therefore, the experimental data support the idea that microtubules are generators of the electromagnetic activity in living cells. However, direct measurement of a single microtubule in a living cell has not been performed yet. The physical mechanism of microtubule oscillations and generation of the field are not fully explained. The polar modes may interact with the free charges and the water molecules inside the microtubule. The resonant frequencies may also depend on electron oscillations in the secondary structure of heterodimers. Nevertheless, interaction between the elastic and electric oscillations seems to be important.

Several mechanisms are utilized for the energy supply to microtubules. The energy is supplied by hydrolysis of GTP to GDP in β tubulins after polymerization,[30,33] motion of motor proteins along microtubules,[20] and very likely also by nonutilized energy liberated from mitochondria.[34,35] Chemical reactions release photons and in this way may supply the energy to oscillations in the UV and visible wavelength regions.

Microtubule oscillations below 1 GHz very likely form only a low frequency component of the whole biological electromagnetic spectral range. Some parts of biological systems may represent resonant circuits which may be excited. A living cell forms a cavity resonator for electromagnetic waves at the frequency of about 10^{13} Hz, which corresponds to a cell of a spherical shape with a diameter about 10 μm.[36] The positions of the mitotic spindle poles may correspond to the nodes of the cavity electromagnetic field and the geometrical shape of polar and kinetochore microtubules to the line of force of the field.[27] Dimensions of the inner microtubule cavity correspond to a soft X-ray resonator.[36]

4. Mitochondria Support Microtubule Oscillations

Mitochondria are multifunctional organelles in the cell. They have different shapes with linear dimension of about 0.5–1 μm and occupy a substantial portion of the cytoplasmic volume of eucaryotic cells. The activity of mitochondria is provided on their inner membrane. The energy released from the foodstuffs is parceled out by mitochondria with utilization of oxygen into small packets for efficient covering of biological needs (the oxidative metabolism of mitochondria). However, mitochondrial function encompasses several fundamental physical processes and cannot be reduced to mere production of ATP and GTP. Utilization of the chemical energy for proton transfer from the mitochondrial matrix to the intermembrane space and proton diffusion into cytosol through holes in the outer membrane is an important intermediate mechanism in the energy production. A layer of a strong static electric field created around mitochondria up to a distance of several micrometers was measured by Tyner *et al.*[37] The static electric field changes the phase of water. Layers of ordered water are formed. Water ordering by a strong electric field is a general phenomenon in nature; water is ordered around charged surfaces. Special layers around microtubules 5–20 nm thick (clear zones) were measured by Amos.[38] Formation of the clear zones was assumed to depend on the negative electrostatic charge at the microtubule surface.[39] The interfacial ordering was studied and described by Zheng *et al.*,[40] Pollack *et al.*,[41] Chai *et al.*,[42,43] and Pollack.[44] Fuchs *et al.*[45–47] and Giuliani *et al.*[48] investigated formation of a floating water bridge between two glass beakers after application of the field by electrodes. The ordered water exhibits separation of charges and loses its viscous damping property.[49,50] Explanation of these findings based on the theory of arrangement of coherent microscopic domains (that exist in water) into macroscopic ordered layers was published by Preparata[51] and Del Giudice and Tadeschi.[52]

A periodic character of the cell development is a general process in nature. The cell cycle has distinct phases. The M phase denotes the process of nuclear division and separation into two cells. The remaining portions of the cell cycle are included into interphase, i.e. the period between two M phases. In the interphase mitochondria are aligned along microtubules in the regions of greatest energy consumption. The strong static electric field around mitochondria may shift oscillations in molecules and structures into a highly nonlinear region.[49,50] Significant reduction of the water viscosity damping of microtubule oscillations is caused by the ordered water around them.[49] Analysis of the effect of a protective layer of the ordered water on damping was performed by Pokorný.[53]

5. Interactions Between Cells

The electromagnetic fields generated by living cells in the frequency region below about 100 MHz may be important in organization of tissues, synchronization of biological processes, and establishment of coherence in low frequency bands. The dimensions of the biological bodies and particular organs are much smaller than

the wavelength of the field. In a medium with relative permittivity about 100, wavelengths at the frequencies 10 kHz and 10 MHz are 3000 m and 3 m, respectively. However, the electromagnetic field generated by a cell depends on the spatial arrangement of microtubules and the way of their excitation in the cell. In an ideal case microtubules form a discrete spherically symmetrical structure. If the oscillations correspond also to spherical symmetry, only a weak electromagnetic field is generated in the direction of microtubule axes at a short distance from the plasma membrane. The polar modes generated around cells by the plasma membrane can mediate interactions between the cells which are not in a direct contact. The discrete spherical symmetry of microtubule oscillations could be disturbed if the cells are in direct contact. The excited microtubule oscillations can generate a tissue field. Due to character of the near field the high intensity of the longitudinal components of the electric field of the microtubule dipoles might be dominant in interactions. The interaction energy was analyzed to assess interactions between oscillating systems. The interaction forces are very small if the frequencies of interacting cells are different as was evaluated by Fröhlich[7] and Pokorný and Wu.[54] The effect of coupling of the Fröhlich's polar modes to the heat bath on the interaction forces was analyzed by Pokorný.[35,55] The interactions are spectral sensitive.

The motor proteins provide essential transport along the microtubules. The directional transport of biological molecules and reaction components in the cytosol cannot be explained on the basis of a random Brownian motion. A combination of electrodynamic deterministic and random forces in the directional transport of mass particles was analyzed.[56] Organization of the living matter might depend on the directional transport.[57] Communication between the brain and various parts of the body could be mediated by streams of photons, which may provide a high capacity information transfer.[58]

6. Cancer Process

Cancer is a multistep and multibranch microevolutionary process. The links that compose the cancer transformation pathway contain disturbances of the biochemical–genetic and physical origin. At the cancer beginning the links comprise a wide spectrum of processes of different nature. Besides chemical and genetic changes caused by different agents, also mechanotransduction[59,60] disturbances may develop into cancer. Therefore, the classification and treatment of cancers based on the processes in the initial links is a complex task. Above it, the cells in their development can change their genetic make-up. But all these processes at a critical stage of development trigger the defect of the oxidative metabolism caused by inhibition of the pyruvate transfer into the mitochondrial matrix.[10] Warburg's experimental research disclosed that all measured cancer tissues displayed the mitochondrial dysfunction.[8] The mitochondrial dysfunction was observed in cancer cells or in the fibroblasts associated with a cancer cell.[11] The experimental results of Jandová *et al.*[12] suggest that the mitochondrial dysfunction in cervical carcinoma develops

in precancerous state. The mitochondrial dysfunction results in the changed energy production and altered behavior of cells, in particular disturbed interaction with other cells leading to local invasion and beginning of tumor generalization. This state is assigned to disturbances of the energy coherent states. The origin of cancer is a problem which is not yet solved. It is assumed that several signal triggers producing cancer have to act on the cell. Changed genes are observed in the initial links before malignant properties appear. Ionic radiation, external mechanical forces, or other external agents may result in a dangerous cancer triggering signal. A mechanical transduction of external pressure or tension can cause the genetic changes and mitochondrial dysfunction too.[59,60] It should be mentioned that cancer might be also set up by chronic decrease of electromagnetic activity causing inaccurate or wrong cellular mechanisms. A unique cancer triggering mechanism has not been revealed yet.

The mitochondrial dysfunction has two modifications which determine the normal and the reverse Warburg effects; transfer of pyruvate to the mitochondrial matrix is inhibited in the cancer cells or in fibroblasts associated with the cancer cells, respectively. There are a few biochemical molecules blocking the pyruvate transfer. In the cancer cells with the normal Warburg effect the pyruvate dehydrogenase complex in mitochondria is regulated by pyruvate dehydrogenase kinases (PDK). This type of cancer cells termed the glycolytic phenotype was described by Bonnet *et al.*[10] McFate *et al.*[61] published that there are four isoforms PDK-1–4. Inhibition of pyruvate processing by mitochondria causes disturbances of the static electric field and the ordered water layer around them leading to increased damping of the microtubule oscillations. The power of microtubule oscillations is lowered and their frequency altered. The interaction forces of the cancer cells with the healthy cells in the tissue are reduced and conditions for generalization of the tumor are prepared.

The Warburg effect link along the cancer transformation pathway is assumed to precede the malignant properties. The idea is based on measurement of the response of the cell mediated immunity to the antigen of lactate dehydrogenase elevating virus (LDV). LDV enhances the level of LDH isoenzymes. The antigen was prepared from serum of inbred mice C3H H^{2k} strain infected with the LDH virus. The response to the antigen was investigated by Jandová *et al.*[12] T lymphocytes were prepared from venous blood of healthy women, patients with cancer and precancerous lesions of cervix. Effects of the LDH virus and the cervical cancer antigen are similar. The results suggest that the mitochondrial dysfunction in the cervical cancer development is caused in the precancerous link of cancer transformation. The mitochondrial dysfunction seems to be an essential condition for the malignant activity of cancer cells.

The cancers with the normal and the reverse Warburg effect form two main groups of cancers. The mitochondrial dysfunction is set up in cancer cells or in their associated fibroblasts. Cancer cells with mitochondrial dysfunction produce only about one half of the cell energy production by the oxidative metabolism.

In healthy cells the oxidative ATP production may be even 100 times greater than the fermentative one. Damadian[62] found by measurement of the nuclear magnetic resonance (NMR) that cancer cells create a less ordered system. He wrote that "the malignant tissues were characterized by an increase in the motional freedom of tissue water molecules". In contrast, Kiricuta and Simplăceanu claimed that the main cause of the differences observed between the spin–lattice and spin–spin relaxation times of the normal and malignant tissue is the higher water content in the latter tissue.[63] NMR relaxation times are characteristic properties that depend on the physical processes of water in the measured system and about 20% increase in volume of water cannot change them. Assuming that the cells contain both the ordered and the bulk water, then the relaxation times are described by the sums of weighted exponential components representing both phases. The differences in the relaxation times between healthy and cancer tissues are about 300%. The measured differences in water content cannot cause significant changes. The main difference results from the viscosity of the ordered and the bulk water. The viscosity of the bulk water with low level of ordering causes large values of the relaxation times and damping of oscillations in microtubules.[49] The diminished static electric field around mitochondria might result in a shift of the microtubule oscillations toward a linear region. Consequently, power of the electrodynamic field is lowered, the coherence diminished, and the frequency spectrum shifted and rebuilt.

Cancers with the reverse Warburg effect were observed by Pavlides *et al.*[11] at breast cancer cells. Since then properties of the novel phenotype of cancers have been described in a large amount of publications (some references are included[64–74]). The epithelial breast cancer cells have fully functional mitochondria and the mitochondrial dysfunction is induced in associated stromal fibroblasts. This pathological process is conditioned by a loss of expression of caveolin-1 in the stroma. The energy rich metabolites (pyruvate, lactate, glutamine, ADMA-asymmetric dimethyl arginine, and BHB — beta-hydroxybutyrate) produced by fermentation are supplied to a cancer cell from the associated fibroblasts with dysfunctional mitochondria. The energy production and power of the electrodynamic field in the cancer cells are high. The microtubule oscillations are shifted to a highly nonlinear region and the frequency spectrum is changed. The energy rich supply from the environment support growth of the cancer cell and its aggressiveness.

The two types of cancers were known and distinguished about thirty years ago by measurement of potential difference of the mitochondrial inner membrane (but these different types of cancers were not connected with the Warburg effect). The membrane potential (negative inside) depends on the distribution of the negative and positive charges connected with the mitochondrial function. Positively charged protons are transferred across the inner membrane. The measurements were performed by a fluorescent method — uptake and retention of positively charged fluorescent dyes (URFD). For instance, the high value of URFD (called hyperpolarization) was measured at a large amount of tumors of ovary, kidney, colon, liver, and other organs showing that a great majority of carcinomas and melanomas are of the glycolytic

phenotype.[75,76] The difference in the mitochondrial membrane potential between the normal cells and the carcinoma cells of at least 60 mV was measured by Modica-Napolitano and Aprille.[77] On the other hand the most significant exceptions have been oat and large cell carcinomas of lung, poorly differentiated carcinoma of colon, lymphomas, sarcomas, and neuroblastomas,[75,76] where low values of URFD were measured. Bonnet *et al.*[10] proved that after treatment of the human cancer cell lines A549 (no-small cell lung cancer), N059 K (glioblastoma), and MCF-7 (breast cancer) by DCA (dichloroacetate), the membrane potentials measured by URFD were reversed to the low values (i.e. mitochondrial normal function was restored). Therefore, the high value of URFD does not indicate a large mitochondrial activity and very likely depends on the distribution of positive and negative ions in the cell (K^+, lactate) and/or the ordered water layer around mitochondria. Nevertheless, measurement of the mitochondrial membrane potential enables us to distinguish the two phenotypes of cancers.

The function of biological organs depends on mutual interactions and cooperation between the cells in the tissue. Generally, the long-range interactions depend on the generated electromagnetic fields, their frequency spectra and spatial patterns. The cancer cell may escape from interactions with the surrounding healthy cells and perform individual activity if its frequency spectrum of the electromagnetic field is rebuilt and shifted[7,54,55] and/or spatial pattern disturbed. The spatial pattern depends on the geometrical arrangement of the cytoskeleton structures, in particular of the microtubules and their excitation. Human nontumorigenic epithelial breast cells have a smaller deformability than the cells with increased metastatic potential — 10 and 30%, respectively.[78] The bioactive lipid SPC that influences the cancer metastasis causes shrinking of the keratin network around the nucleus[79] and consequently may cause diminished interactions between the cells based on the microtubule oscillations. It is not clear whether such keratin defects are connected with shrinking of the nuclear membrane (wrinkling) used as one of the important diagnostic markers in examination of gynecological cancers. The interaction forces between cancer cells may differ from those between healthy cells or between a healthy and a cancer cell. The force effect together with disturbances of the intercellular matrix may constitute an essential part of the local invasion and metastasis. This process is well described and referred to as the epithelial-to-mesenchymal transition.

Escape of a cell from the tissue subjection and its independent activity is a basis of the malignant properties. The cancer cells with the mitochondrial dysfunction have a lower biological activity than healthy cells. The cancer cells with fully functional mitochondria and a supply of energy rich metabolites display a higher biological activity than healthy cells and a high aggressiveness (but together with fibroblast very likely a lowered total energy of the coherent states far from the thermodynamic equilibrium). The effects of mitochondrial dysfunction and overfunction can be assessed on the basis of the electrodynamic fields generated by microtubules. The deviation of the power of the microtubule oscillations to lower or higher values results in corresponding frequency shifts and a loss of the interaction

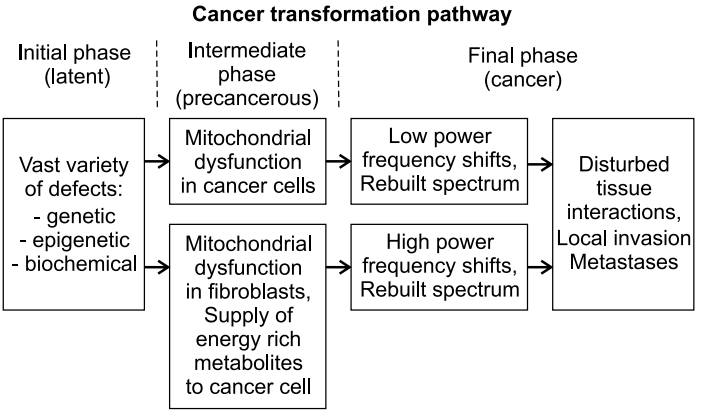

Fig. 1. A scheme of the cancer transformation pathway. The pathway is divided in three main phases containing (a) chemical, genetic, and epigenetic disturbances (the initial phase), (b) formation of mitochondrial dysfunction in cancer cells or associated fibroblasts (the intermediate phase), and (c) changes of power and frequencies and consequent malignant deviations (the final phase).

forces with the cells in the healthy tissue. The absorption resonant frequency of some cancer tissues were found at about 465 MHz.[23] The frequency of the microtubule oscillations depends on the nonlinear characteristic of the microtubule oscillators. If the force constant in the potential valley increases with the decreased excitation power then the frequency 465 MHz of the glycolytic phenotype cancer corresponds to the shifted spectral lines of the healthy cells in the frequency band below 200 MHz. A schematic plot of the cancer transformation pathway (including frequency shifts) is shown in Fig. 1.

7. Discussion

Chemical, genetic, and physical mechanisms make up tools for biological functions. These mechanisms by themselves represent manifestation of a system whose living essentials are not yet clear. The chemical reactions and the physical processes of biological systems may exist in the inanimate world too but all of them together demonstrate the animate system. Cells subjected to the tissue ordering are very likely capable of acting like independent entities. In the tissue the cell performs mechanistic activities which can be described in terms of chemical signaling, transfer of information encoded in the genome for production of proteins, and other operations under general control executed by the tissue, the brain, and the rest of the body. The cell is an obedient machine which under control does not express its possible independence. However, the cell performs all its duties under internal instructions — very likely programs inscribed in internal structures. The nuclear DNA contains information for the material building in the protein coding part (which occupies a fraction smaller than 2%). The rest of the human genome forms the noncoding sequences. A few percent of the genome contains highly conserved

parts of noncoding DNA which is an evidence of a strong evolutionary pressure. It may be assumed that the noncoding part of DNA contains a wide spectrum of information for chemical reactions and physical processes in the cells. The essential physical parameters for establishment of the coherent oscillations of cells in the tissue and the whole body are the power and the frequency of oscillations in the cellular structures. Fröhlich assumed the generating structures in the plasma membrane.[6] Del Giudice *et al.*[80] derived that the quantum self-focusing causes confinement of the electromagnetic waves to signals in a region whose dimension corresponds to the microtubule internal diameter. The idea of the coherent excitation in the cytoskeleton was analyzed by Hameroff[81] and Fröhlich included this contribution into the volume devoted to the biological coherence. Penrose[82] related consciousness to the action of the cytoskeleton and to microtubules in particular. Generation of Fröhlich's polar vibrations in microtubules was proposed by Pokorný *et al.*[30] The oscillations in the tubulin heterodimers in the microtubules interact with the ordered water and the free charges in the water inside the microtubule cavity that conditions the microtubule function.[32] The ordered water around microtubules provides low damping[49]and may also participate in the coherent oscillations. (The layers of the ordered water are formed by a strong static electric field, for instance around the charged surfaces of protein structures,[44] mitochondria,[50] etc.) Therefore, the physical properties of heterodimers and the level of their excitation belong to the essential parameters.

The frequency depends on the potential valleys of the heterodimer oscillators. The tubulin heterodimers encoded by the genome display a variety of conformation states (caused by dipolar arrangement) dependent on the electric parameters.[83] Different dipolar arrangements should result in different potential valleys. The measured spectra of the resonant frequencies of oscillations in the microtubules in the frequency band below 2 GHz suggest a nonlinear nature of the potential valleys which causes dependence of the frequency of oscillations on the power.[32] Besides that, the properties of the potential valleys may be changed by the static electric field created by mitochondria along the microtubules and the resonances depend also on the interaction of oscillations with the mobile charges in the ordered water filling in the microtubule cavity. The cell should maintain the frequency and the power of oscillations at the required values either through interaction with the other cells or by regulation. The regulation process needs frequency and power standards. The sequences of bases (adenine, etc.) might be inscribed into the noncoding part of DNA and after a convenient translation could represent the standards for regulation. DNA in the nucleus represents the ROM memory of the cell. A program of the cellular activity might be an issue of evolution, development, and storage in the memory. Mechanisms of its realization could depend on the microtubules which are engaged in a number of cellular activities. A single microtubule has a memory capacity of about 500 bits.[83] The total capacity of the digital memory of microtubules in a cell is about 20 kB. Therefore, microtubules could form a RAM memory. Microtubules have another remarkable property. They behave like

biomolecular transistors capable of amplifying electric signals.[84] Microtubules with a centrosome could perform a role of a processing unit. Therefore, the cell seems to represent a functional system whose activity is programed and experience stored in the memory.

The malignant properties of cancer cells are created after significant disturbance of the oxidative metabolism. The power and the frequency of the microtubule oscillations are altered, which leads to a loss of interaction in the tissue and independent behavior of the cell. This pathological state may be caused by the defects of the coding and/or noncoding sequences of the genome. The former case leads to pathological production of some proteins, the latter case to defective mechanisms, functions, or setting some incorrect parameters (e.g. the frequency). Nevertheless, a parasitic consumption of the energy may also lead to changes of the energy level and loss of interaction of a cell with the tissue. Seyfried and Shelton[85] published a hypothesis that the mitochondrial dysfunction is a primary cause of cancer. The hypothesis is in contradiction with the observation that mitochondrial dysfunction is formed in the period of precancerous lesions developed after previous changes. On the other hand the Seyfried and Shelton hypothesis indirectly supports the idea that the lactate dehydrogenase elevating virus (LDV) is somehow connected with origin and/or development of the cancer process. LDV establishes lifelong persistent viremia in mice, parasites on the energy system, and is observed as a dark particle at the mitochondria.[12] The possible role of LDV in the cancer origin, course, and progress is not clear. LDH virus antigen elicits a response of the cell mediated immunity of T lymphocytes prepared from venous blood of the patients with malignant tumors (breast, gynecological, laryngeal and pharyngeal).

The microtubule oscillations and the electromagnetic field might be disturbed by increased conductivity in the cell. Asbestos cancerogenicity (mainly production of mesothelioma) is explained by the capability of the asbestos fibres to short-circuit distant parts of the cell with different levels of the electromagnetic field. Asbestos may form optic fibres for the cellular field[86] and/or conductive wires after adsorption of specific proteins and molecules containing iron atoms at the fibres surface.[87]

The high values of URFD measured at the mitochondrial inner membrane in cancer cells with the normal Warburg effect are explained by hyperpolarization. It contradicts the fact that mitochondria are dysfunctional. The real membrane potential corresponding to the proton transfer is smaller than in a healthy cell. The value of the measured potential rather corresponds to the increased amount of the lactate produced as a result of inhibition of the pyruvate transfer into the matrix and reaction of the lactate dehydrogenase enzyme. The production of negatively charged lactates might in a final effect result in an increased number of hydrogen ions to maintain electroneutrality. It should also be mentioned that the experimental data from URFD measurement were interpreted without analysis of the effect of the ordered water layer around mitochondria. The water ordering is not significant if the membrane potential and the intensity of the electric field are

low. All transferred protons are concentrated at the membrane. For higher membrane potential an ordered layer of water is built. The protons may be distributed in two layers. The inner layer is at the membrane, the outer layer at the outer rim of the ordered water. Therefore, only a part of the membrane potential is measured. This might be the case of the healthy cells and the cancer cells with the reverse Warburg effect.

Measurement of the electrodynamic activity of living cells is a challenge for nanotechnology. The power of the oscillating field is extremely low. The whole cell processes a power of about 0.1 pW.[88] A part of the power may be transformed into the polar modes in individual microtubules. Each of about 400 microtubules in a cell might be excited by a power of the order of magnitude 0.1 fW. The quality factor of a microtubule is very likely not much less than 100 (determined from data of Sahu *et al.*[32]) and the total power which may be possibly released from oscillations in the microtubule cellular structure should correspond to about 10 fW. Microtubules in the cell are assumed to be arranged in a symmetrical system (for instance discrete spherical symmetry in a spherical cell) and excitation of the oscillations should correspond to the same symmetry. In this case the emission losses are low. If the power measured at the plasma membrane depends only on the electrodynamic oscillations of a single microtubule, a power of the order of magnitude of 0.1 fW or lower could be detected. Another requirement concerns the dimension of the sensor contact. The electrodynamic field of an individual microtubule bound to a structure at the membrane could be measured at a region with the linear dimensions smaller than about 100 nm. Measurement should be provided at a "biological" temperature.

The mitochondrial dysfunction is a key point in the cancer development. It is a point of transition to malignancy. A large variety of the genetic, epigenetic, and biochemical disturbances result in the dysfunction of mitochondria in cancer cells or in their associated fibroblasts. Both phenotypes of cancer cells (i.e. cancer cell with dysfunctional and fully functional mitochondria) are protected against apoptosis. Treatment of cancers at the link of the mitochondrial dysfunction seems to be promising. A normal function of mitochondria in cancer cells with the Warburg effect could be restored by blocking PDKs (or their production) inhibiting the pyruvate transfer into the mitochondrial matrix. A normal function of fibroblasts in cancers with the reverse Warburg effect could be achieved by cutting off the pathological signaling from the cancer cell to fibroblasts, transport of the energy rich metabolites from fibroblasts to the cancer cell, and restoring a normal mitochondrial function in fibroblasts. After restoration of a healthy state the cells do not necessarily have to continue in their normal function. A restored cancer cell which has been damaged to a large extent would enter the apoptotic process. However, the cancer cells of both phenotypes could also return to the pathological cancer state. It may signify that the conditions for creation of the pathological state remain unchanged and that they might be stored in ROM and/or RAM memory of the cell. But even temporary transition of cells from the cancer to the healthy

state could make possible an effective treatment of cancers of the fourth stage. In general, targeting mitochondrial link of the cancer transformation can represent a big step forward in the cancer treatment.

8. Conclusion

One of the main differences between the animate and inanimate systems is a coherent state far from the thermodynamic equilibrium dependent on the energy supply. In multicellular bodies this coherent nonequilibrium state depends on the oxidative metabolism of mitochondria which transforms the chemical energy into a convenient form and adjusts the conditions for excitation of the coherent polar oscillations in microtubules. Mitochondria — an almost universal part of the eucaryotic cells — are multifunctional organelles which in the process of energy transformation produce layers of a strong static electric field and ordered water around them. These layers make possible low damping of the polar oscillations in microtubules and their shift into a highly nonlinear region. The energy stored in the polar oscillations in microtubules forms a low frequency component of the coherent state far from the thermodynamic equilibrium of the biological system. Microtubules are one of the oscillating structures generating the cellular electromagnetic field whose function includes participation in the interactions with the surrounding cells in the tissue. Excitation of polar oscillations is crucial for multicellular organisms.

Disturbances of the mitochondrial function, the cytoskeleton structure, and the oscillations in microtubules cause defects of the coherent state far from the thermodynamic equilibrium which endangers life. An important link of the cancer transformation pathway contains mitochondrial dysfunction in the cancer cells (the normal Warburg effect) or in the fibroblasts associated with the cancer cells (the reverse Warburg effect). This transformation produces inhibition of the apoptotic function so that the cancer cells are immortal. The mitochondrial dysfunction resulting in disturbances of the electromagnetic field leads to an independent behavior of the cell in the multicellular body. Malignancy is created. Cancer is a pathology of the coherent state far from the thermodynamic equilibrium. The treatment should be primarily targeted to restore the mitochondrial function.

The cells subjected to the tissue seem to be able to perform activity of an independent living entity. Instead, the cell carries out mechanistic work under general control of the tissue assembly of cells, the brain, and the rest of the body. The cell is a tissue-abiding machine. But all its duties seem to be performed under internal programs stored in the genome in its coding and noncoding parts. DNA in the nucleus represents a ROM of the cell. The microtubules can store information and may be considered as a RAM type memory. The microtubules are also capable of providing a role of the processing unit. A program for the cell functions and processes is stored in the memory and very likely could be changed on the basis of the cell experience or random events. Cancer cell could be also governed by a changed memory program.

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