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Biophysical Cancer Transformation Pathway

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Coherent vibration states in biological systems excited in nonlinear electrically polar structures by metabolic energy supply were postulated by H. Fröhlich. Fröhlich's requirements for coherent vibrations and generation of electromagnetic field are satisfied by microtubules whose subunits are electric dipoles. Static electric field around mitochondria and "wasted energy" efflux from them provide nonlinear conditions and coherent excitation. Numerical models are used for analysis of coherent vibration states.

A hypothesis is presented that dysfunction of mitochondria (i.e., extinction of the zones of the static electric field and of the efflux of "wasted energy") and disintegration of the cytoskeleton on the pathway of cancer transformation result in disturbances of coherence of the cellular electrically polar oscillations and of the generated electromagnetic field with consequences in cellular organization and interactions between cells. Local invasion, detachment, and metastasis of cancer cells are subsequent events of disturbed electromagnetic interactions.

Keywords Cancer transformation; Biophysical cancer pathway; Biological electromagnetic field; Coherence in biology; Mitochondria; Microtubules; Fröhlich's hypothesis.

Introduction

The most fundamental mechanisms and processes acting inside cells and between cells are disturbed or damaged by cancer. Cancer changes the inner processes in cells as well as their mutual interactions and social behavior in the tissues. Cancer transformation pathway is a multi-step and multi-branch microevolutionary process triggering many pathological events of biochemical, biophysical, and biological character (Alberts et al., 1994). Clinically diagnosed cancer is the last evolution phase characterized by progression along the sequence of pathological events—proliferation, local invasion, detachment of individual cancer cells, and establishment of metastasis. A general feature of cancer is proliferation. The structure of the initial non invasive proliferating cancer very often lacks the typical organization pattern of the corresponding healthy tissue (Abercrombie and Ambrose, 1962). It is also assumed that the growth activity may be connected with diminished adhesiveness. Classical oncologists assumed that

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local invasion—burrowing of cancer cells into immediate surroundings—is rather a result of active locomotion than of a passive transport (for instance not a result of pressure inside the tumor). Cancer cells display changes of the cytosol, of the cellular membrane, loss of cohesion and contact inhibition, and tendency to separation. Cellular adhesiveness is an important property for keeping tissues in ordered state. Loss of adhesive forces between cancer cells leads to detachment of cancer cells and their spreading in the whole body by passive transport. The cancer cells become widely disseminated. Arrest of cancer cells in other parts of the body very often is organ specific. Therefore, a significant feature of cancer cells is their diminished and deformed adhesiveness.

Alteration of proto-oncogens to oncogens resulting in production of protein kinases is linked with the beginning of cancer. Epigenetic origin of cancer is supposed to be a rare event. In healthy cells phosphorylation is a ubiquitous regulation mechanism. In cancer cells protein phosphorylation is different and causes deviations from normal processes. Hydrogen atom in the terminal OH group in the side chain residues of serine, threonine, and tyrosine is replaced by a phosphate group (inorganic phosphate). The phosphate group has about 80 times greater mass than the hydrogen atom and forms an electric multipole with negative charge at the surface. The negative charge of the phosphate group interacts with positive charges of amino acid side chain residues inside the protein (changing protein conformation) and in the surrounding medium (causing increased coupling and energy transfer from oscillating systems). Regardless of giant progress in the biochemical research and discovery of complicated systems of biochemical cancer transformation pathways, important processes of biological activity and cancer malignity are not well understood.

Fröhlich formulated hypothesis that in living matter some modes of motion are strongly excited and remain far from thermal equilibrium forming coherent state, and that the underlying mechanism is based on nonlinear interactions of oscillating elastic and polarization fields (Fröhlich, 1968a, 1968b, 1969, 1973a, 1973c, 1977b, 1977c, 1980). Due to nonlinear interactions, energy supplied from metabolic sources is not thermalized but accumulated in some oscillation modes. Coherent polar oscillations are excited and a coherent electromagnetic field generated. Fröhlich conjectured that disturbances of the electromagnetic coherent states lead to evasion of cancer cells from control and regulation in the tissue (Fröhlich, 1978).

Fröhlich's mechanism has a parallel in solid state ionic crystals. Synchronized motion of natrium and chloride ions in NaCl crystals can be excited by a mechanical stroke (Reed et al., 2006). The mechanical shock wave interacts with polarization wave generated by motion of charges. Coherent electromagnetic signals greater than noise are generated in the frequency range from 10–50 THz. Generation of coherent electromagnetic field seems to be a general property of electrical polar structures subject to mechanical vibrations under nonlinear conditions.

Fröhlich's hypothesis revolutionized view on biological systems. Coherent biological electromagnetic field mediates long-range interactions and control (Fröhlich, 1969, 1970, 1973b, 1973d, 1975, 1977a). Energy supply and its accumulation in vibration modes is an indispensable condition for action of specific forces (Fröhlich, 1972, 1973c, 1977c, 1977d). Therefore, biological electromagnetic field generated by electrically polar structures is assumed to have an essential function in organization of biological systems, polymerization of intracellular structures, formation of morphological features, directed transport of mass and charge, organization of biological

reactions, and interactions between cells (Pokorný, 2001, 2003, 2004; Pokorný and Wu, 1998; Pokorný et al., 2005a, 2005b). Cancer transformation may change the biological electromagnetic field. Dysfunction of mitochondria and disintegration of the cytoskeleton on the cancer transformation pathway signify the disablement of the structures involved in generation of the electromagnetic field.

Direct and indirect measurements of the electromagnetic field generated by biological systems support Fröhlich's hypothesis. Small dielectric particles with high permitivity are attracted to cells by dielectrophoretic forces (Pohl, 1978, 1980; Pohl et al., 1981; Roy et al., 1981; Lamprecht and Hölzel, 1987; Hölzel and Lamprecht, 1994). Yeast cells in the M phase display the greatest electromagnetic activity (Pohl et al., 1981). Interaction between baby hamster kidney (BHK) cells is mediated by electromagnetic field in the red and near infrared region (Albrecht-Buehler, 1992). The Swiss 3T3 cells are able to sense the near infrared radiation and to determine direction of individual sources (Albrecht-Buehler, 1991). Formation of aggregates of $3T3_x$ cells (a variant derived from 3T3 cells) is conditioned by electromagnetic interaction in the near infrared range (Albrecht-Buehler, 2005). Interaction forces between red blood cells act up to a distance of about 1 μm (Rowlands, 1983, 1988; Rowlands and Sewchand, 1982; Rowlands et al. 1981, 1982; Sewchand and Rowlands, 1983). Coherent vibrational motion in the bacterial photosythetic reaction centers was measured at 15 and 77 cm^{-1} using femtosecond laser spectroscopy (Vos et al., 1991, 1993, 1994a, 1994b, 1994c, 1998, 2000).

Mechanical oscillations of erythrocyte membranes were measured at low frequencies below 30 Hz (Levin and Korenstein, 1991; Bitler and Korenstein, 2004; Tuvia et al., 1997, 1998, 1999). Pelling et al. measured mechanical oscillations of yeast cell membranes in the acoustic frequency range (around 1 kHz) using atomic force microscope. The measured amplitudes of oscillations were of about 3–4 nm (Pelling et al., 2004, 2005). Electromagnetic activity and mechanical oscillations of yeast cells are measured at small patches of cellular membranes with linear dimension smaller than about 100 nm (Pokorný et al., 2008). Distribution of oscillations on the membrane may have a zonal character-like spherical harmonics structure (Pokorný et al., 1991).

Measurement results of electromagnetic fields of living cells represent only a limited picture of a wide variety of possibilities in nature but it proves existence of electromagnetic fields and interactions mediated by them. The role and function of the biological electromagnetic field have to be an object of experimental research in the future. This article presents analysis of a possible role of the electromagnetic fields in cancer cells.

Nonlinear Systems

Nonlinear systems have special properties. Nonlinear oscillators perform spectral transformation of oscillation energy (up and down conversion along the frequency scale) and transformation of incoherent excitation to coherent oscillations. The Duffing oscillator, an example of a nonlinear dynamic system, is described by the equation

$$\ddot{x} + \beta\dot{x} + x + x^3 = F(t), \tag{1}$$

where x, $\dot{x}$, and $\ddot{x}$ is displacement, its first, and second derivatives, respectively, β is the damping coefficient, and $F(t)$ is the driving force. Without the cubic term x^3,

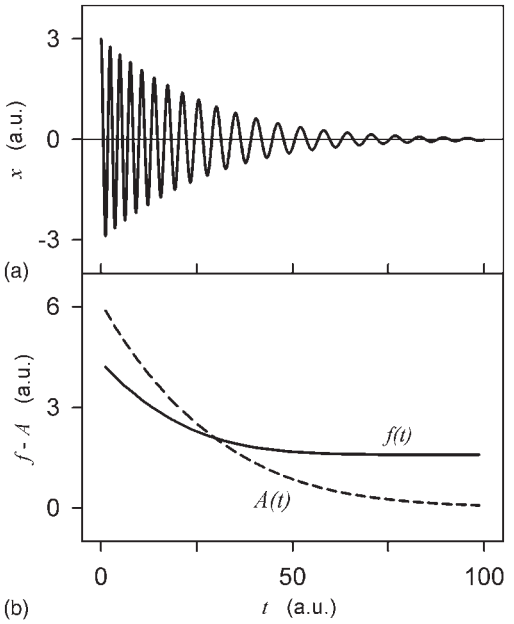


Figure 1. Nonlinear oscillations without a driving force (Duffing oscillator). (a) Displacement x; (b) amplitude A and frequency f, as a function of time.

Eq. (1) represents a linear damped oscillator. Figure 1a shows displacement x, and Figure 1b amplitude A and frequency f of the Duffing oscillator as a function of time t (without a driving force, i.e., $F(t) = 0$). In contrast to a linear oscillator the frequency of oscillations is not constant and dependence between amplitude and frequency is nonlinear. Figure 2a shows random driving force $F(t)$ exciting the oscillator, Figure 2b displacement x, and Figure 2c amplitude A and frequency f as a function of time t (driving force of five random walk steps excites the oscillator at each elementary time increment). Oscillations are partially coherent. Frequency and amplitude display random oscillations around average values. The properties of the oscillator depend on the nonlinear cubic term x^3. Nonlinear interaction between elastic and electrical polarization oscillations is not included.

Fröhlich's Theory of Polar Vibration Modes and Coherent States

Fröhlich considered nonlinear interaction between elastic and electric polarization field excited by metabolic energy supply (Fröhlich, 1973a, 1977c, 1980). The longitudinal polarization waves have discrete spectrum of normal modes whose frequencies ν_i are given by

$$\nu_1 \leq \cdots \leq \nu_i \leq \cdots \leq \nu_z \quad \text{where } I = 1, 2, 3, \ldots, z. \tag{2}$$

Energy transfer between vibration modes of the polarization waves may be described by the rate equations (Fröhlich, 1968a, 1968b, 1980)

$$\begin{aligned} \dot{n}_i =& s_i - \phi_i[n_i \exp(\beta\nu_i) - (n_i + 1)] \\ & - \sum_j \chi_{ij}[n_i(n_j + 1)\exp(\beta\nu_i) - (n_i + 1)n_j \exp(\beta\nu_j)], \end{aligned} \tag{3}$$

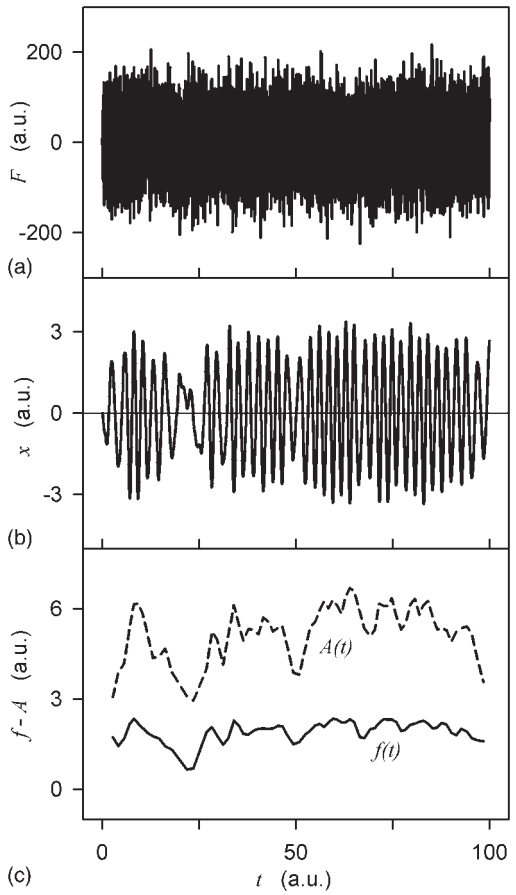


Figure 2. Nonlinear oscillator with a random driving force. (a) Random driving force F; (b) displacement x; (c) amplitude A and frequency f, as a function of time.

where n_i is the occupation number of the i-th normal mode, s_i is the number of energy quanta supplied in unit time from the energy source (rate of energy supply), ϕ_i and χ_{ij} are the linear and the nonlinear transition probabilities, respectively, and $\beta = h/kT$, h is the Planck constant, k is the Boltzmann constant, and T is the temperature. A stationary solution of Eqs. (3) may be derived for $\phi_i = \phi$, $\chi_{ij} = \chi$, and $s_i = s$ in the form

$$n_i = A\frac{1}{\exp[\beta(v_i - \mu)] - 1}, \tag{4}$$

where μ is the excitation potential ($0 \leq \mu \leq v_1$). For $v_1 \sim \mu$ energy condensed in the lowest frequency mode may be high. The stationary solution (4) displays energy condensation in the lowest frequency mode, which is a fundamental property of Fröhlich's vibration system.

Effects of various parameters and different conditions on vibration systems may be assesses by numerical analysis. Coupling of the oscillation system to the heat bath may depend on the condensed energy. We will assume that ϕ_i (χ_{ij}) have the same

values for all the modes ($\phi_i = \phi$ and $\chi_{ij} = \chi$) and that the ϕ transition probability depends on the occupation number of the lowest frequency mode in the form

$$\phi = \phi_0 \exp\left[\left(\frac{n_1 - n_{01}}{n_{\max}}\right)^p\right], \tag{5}$$

where n_{01} is occupation number in the thermodynamic equilibrium, $n_{\max}$ is the limit value of the occupation number in the lowest frequency mode (600 is used), and ϕ_0 is the coefficient of the linear transition probability. The parameter p determines the degree of the nonlinear dependence of the transition probability ϕ on excitation. The nonlinear transition probability is assumed to be given by the relation $\chi = 0.1\phi_0$.

Relation (3) is used for numerical modeling of the Fröhlich vibration systems. Figure 3 shows excitation of models of vibration systems (Pokorný, 2006; Pokorný et al., 2008). Frequencies of the vibration modes are in the range from 0.1–4 THz (i.e., in the mm and submm wave range). The χ term in Eq. (3) describes energy transfer between modes with different frequencies with dominant energy flow downwards to the lowest frequency mode. Energy condensation in the lowest frequency mode depends on energy supply to and on energy losses from the system. The lowest frequency mode is excited if the energy supply is sufficiently high (Figure 3a).

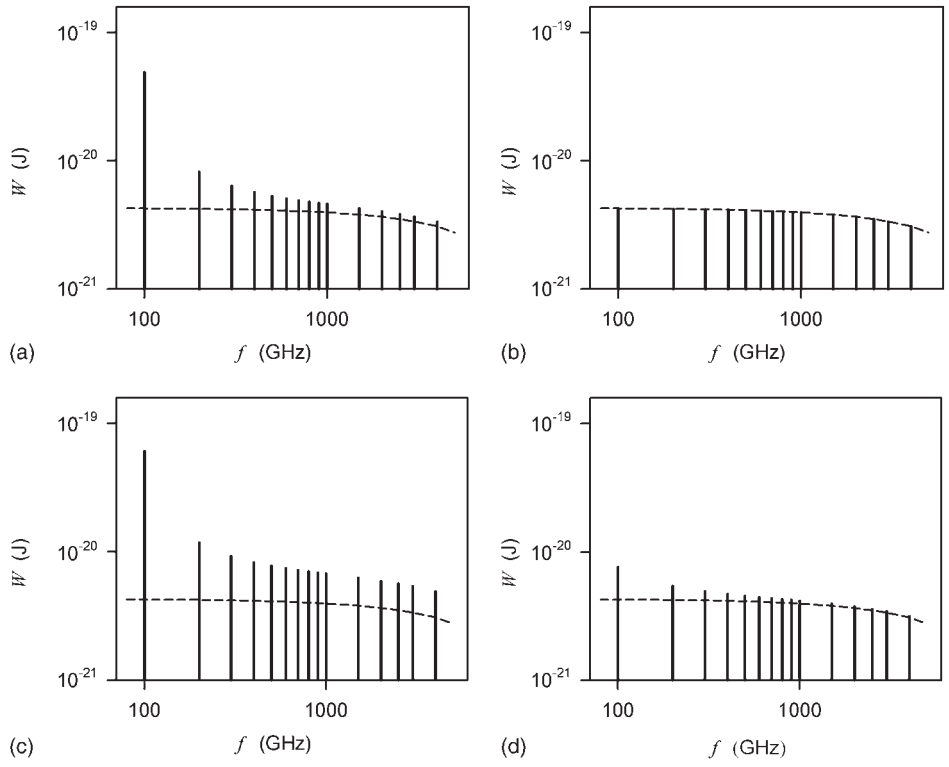


Figure 3. Energy W as a function of frequency f of normal modes of Fröhlich's vibration systems. Frequency range is from 0.1–4 THz, $n_{\max} = 600$, $p = 4$. Resulting energy flow is downwards along the frequency scale. The dashed lines denote the thermodynamic equilibrium values. After (Pokorný, 2006; Pokorný et al., 2008): (a) $\phi_0 = 0.2\,\mathrm{s}^{-1}$, $s = 1\,\mathrm{s}^{-1}$; (b) $\phi_0 = 0.2\,\mathrm{s}^{-1}$, $s = 0.01\,\mathrm{s}^{-1}$; (c) $\phi_0 = 0.01\,\mathrm{s}^{-1}$, $s = 1\,\mathrm{s}^{-1}$; (d) $\phi_0 = 7.5\,\mathrm{s}^{-1}$, $s = 1\,\mathrm{s}^{-1}$.

Some higher frequency modes may be excited above the thermodynamic equilibrium too. At low excitation the thermodynamic equilibrium energy levels are not exceeded (Figure 3b). The effect of coupling of the vibration system to the heat bath is shown in Figures 3c and d. Condensation of energy in the lowest frequency mode is diminished for high damping of the system (Figure 3d).

Dysfunction of Mitochondria

Organization of living cells is conditioned by energy supply from metabolic energy sources. Basic processes of life are connected with energy production and consumption. Glycolysis and mitochondrial oxidative reactions are energy producing chemical processes. A schematic picture of the energy production systems in a cell and function of a mitochondrion is shown in Figure 4. Pyruvate, the final product of glycolysis, and the fatty acids are selectively transported into the mitochondrial matrix. Pyruvate dehydrogenase (PDH) enzymes converts pyruvate to acetyl CoA which, along with acetyl

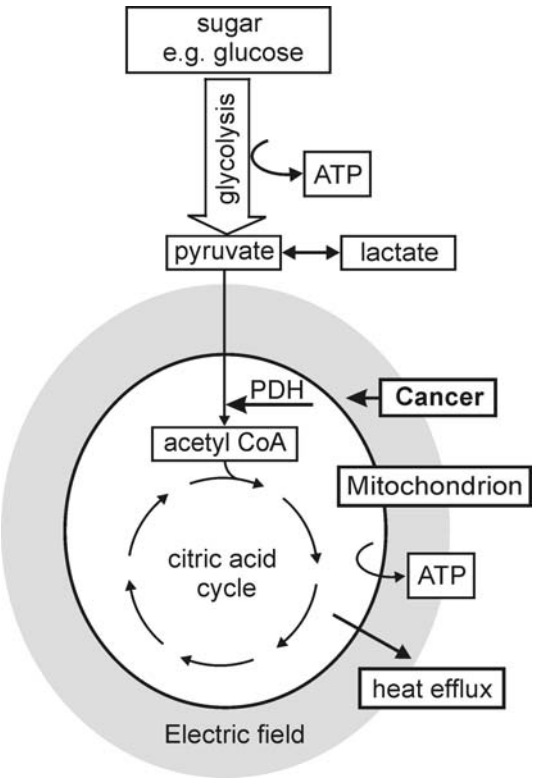


Figure 4. A schematic picture of energy production system in a cell (glycolysis followed by mitochondrial oxidative reactions). The grey region denotes a zone of the static electric field generated by a mitochondrion up to a distance of the order of magnitude of 1 μm (the static electric field depends on pumping of protons into the intermembrane space). In a cancer cell mitochondrial activity is reduced. PDH enzyme family in a cancer cell is dysfunctional due to phosphorylation by the cancer pyruvate dehydrogenase kinase (the key point of cancer transformation is denoted by the arrow and inscription "Cancer"). Entry of fatty acids into a mitochondrion and β-oxidation are not shown.

CoA from fatty acid β-oxidation, is fed to citric acid cycle. More than about 40% of acetyl CoA energy is stored in ATP (adenosine triphosphate) produced by mitochondrial oxidative mechanism (Figure 4). The remaining energy—"wasted energy"—(nearly 60% of acetyl CoA energy) is liberated from a mitochondrion by heat efflux (Alberts et al., 1994). But mitochondria emit radiation too (Batyanov, 1984, 1988, 1995). "Wasted energy" flows out from mitochondria assembled around microtubules, may be absorbed by them and excite microtubular vibrations. Therefore, energy supply to Fröhlich's vibrations may be comparable with the energy stored in ATP.

Besides energy production a functional mitochondrion generates a zone of static electric field around it (a grey zone in Figure 4). Electric field was measured by fluorescence particles of 30 nm in diameter. Spectral emission from the particles depends on the intensity of the electric field (Tyner et al., 2007). Intensity of the electric field at the outer membrane of the mitochondrion is shown in Figure 5 (mean values and standard deviations—evaluated from the data published in (Tyner et al., 2007). Intensity of the static electric field has measurable values up to a distance of several μm's from the outer mitochondrial membrane. As the mitochondria may occupy about of 20% of the volume of the cell, the mitochondrial static electric field fills up nearly the whole remaining volume (cytosol in the cell has to be strongly polarized). Theoretical curves of the intensity of the static electric field as a function of the distance from a mitochondrion are plotted in Figure 6. Intensity of the field depends on concentration of hydrogen ions (protons) in the intermembrane space and their diffusion across the outer membrane. The static electric field of mitochondria may be important for creation and enhancement of nonlinear conditions in microtubules and other cytoskeleton structures.

Oxidative energy production (in mitochondria) is supressed by cancer transformation and the vast amount of energy production is switched to glycolysis in cytoplasm of the cell—Warburg effect (Warburg et al., 1924; Warburg, 1956).

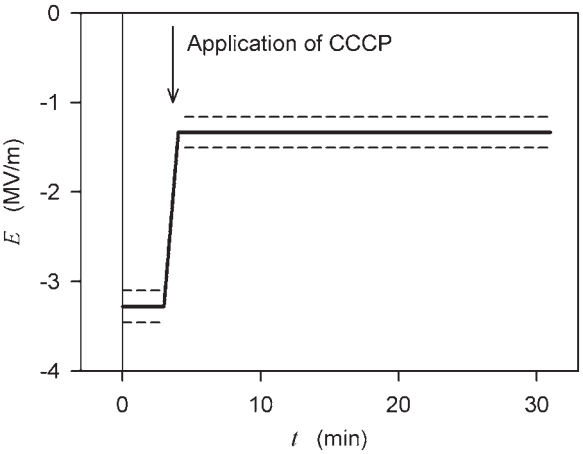


Figure 5. Intensity E of the static electric field (mean values and standard deviations) at the outer membrane of a mitochondrion versus time t measured by fluorescent particles. The intensity decreases after the addition of CCCP (carbonyl cyanide 3-chlorophenylhydrazone) at time 3 min and 40 s after beginning of measurement. The measured data very likely indicate the intensity values inside the fluorescence particles. Evaluated from the data published by Tyner et al. (2007).

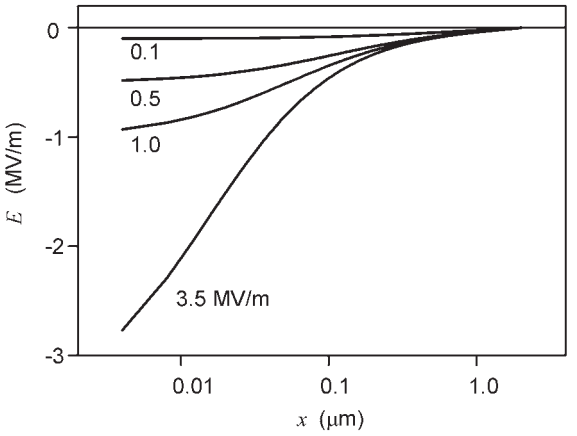


Figure 6. Dependence of the intensity E of the electric field as a function of distance x from a mitochondrion. Particular E curves are evaluated for different density of protons in the intermembrane space. The maximum values of E are assumed at the inner membrane.

Cancer pyruvate dehydrogenase kinase (PDK) blocks activity of PDH (Figure 4). Structure and functioning of mitochondria are changed. Protons are not pumped across the inner membrane into intermembrane space. Dysfunction of mitochondria is accompanied by hyperpolarization of the mitochondrial membrane potential, by extinction of the zone of the static electric field around mitochondrion, and by interruption of ''wasted energy'' efflux. It is proved that alterations in mtDNA (mitochondrial deoxyribonucleic acid) and respiratory activity abnormalities appear to be a general feature of malignant cells (Carew and Huang, 2002). For instance, the function of mitochondria is repressed in human liver, kidney, and colon carcinogenesis (Cuezva et al., 2002). Energy substrate availability could play an important role in mitochondrial dysfunction. Defective mitochondrial system in cancer cells can be improved by changing substrate availability (Rossignol et al., 2004). Iron-sulfur clusters processes in mitochondria are important biosynthetic pathway of life (Lill and Mühlenhoff, 2005), but their role in diseases associated with iron-sulphur protein defects is not yet fully understood.

Frataxin can activate mitochondrial energy production (Ristow et al., 2000). Formation of frataxin increases the activity of the electron transport chain, the mitochondrial membrane potential, and ATP production (González-Cabo et al., 2005), and diminishes malignant transformation in vitro (Schoichet et al., 2002). Impaired mitochondrial function and tumor growth is connected with disruption of frataxin expression (Thierbach et al., 2005). In cancer cells. blockade of ATP production in mitochondria is caused by phosphorylation of PDH enzyme family (converting pyruvate to acetyl CoA) by PDK. The ability of mitochondria to generate energy is booted by DCA (dichloracetate) which activates PDH (Bonnet et al., 2007). Functioning mitochondria help to restore the normal cellular functions and to switch on the apoptosis of aberrant cells.

Biological electromagnetic field is assumed to have an essential role in biological systems and the structural role of the oxidative energy production assumed by Warburg (i.e., the role of mitochondria) may be connected with the respiratory activity and ''wasted energy'' efflux and with the zone of the static electric field around them.

Disintegration of the Cytoskeleton

Cytoskeleton is composed of actin filaments, intermediate filaments, microtubules, and associated proteins. Cytoskeleton is an organization structure of the cell participating in cell motility, ribosomal and vesical transport, mitosis, and transduction of pressure and tension. Elastic modulus of living cell is determined by the state of the cell and can be changed in dependence on internal cellular organization, on biochemical conditions, and on pathological state. The cytoskeleton functions are well organized, regulated, and synchronized. Morphological changes caused by the cytoskeleton on the pathway of malignant transformation are used for cancer diagnosis. Cancer evolution induces cytoskeleton defects before malignant properties of the cell are created.

Microtubular structure satisfies conditions for excitation of Fröhlich's coherent electrical vibrations. Tubulin heterodimes, the building subunits of microtubules, are electric dipoles with large electric dipole moment, greater than 1000 Debye—10^{-26} Cm (Satarić et al., 1993; Tuszyński et al., 1995, 2005). The structure is nonlinear and the binding energy between α- and β-tubulins in a heterodimer differs from that between heterodimers in the protofilament. Nonlinear properties also depend on the static electric field created by mitochondria. Energy is supplied to microtubules from hydrolysis of GTP (guanosine triphosphate) in the β-tubulin after polymerization, by motor proteins moving along microtubules, and by absorption of "wasted energy" flowing out from mitochondria. The "wasted energy" efflux very likely makes up the main part of energy supply.

Microtubules are structures with anisotropic properties. Young's modulus along the microtubular axis is about $1.32 \times 10^9\,\mathrm{Nm}^{-2}$, effective lateral elastic modulus (for a force acting in the direction perpendicular to the axis) is $4 \times 10^6\,\mathrm{Nm}^{-2}$, and the shearing modulus vary in the limits from $53\,\mathrm{Nm}^{-2}$ to $0.5 \times 10^6\,\mathrm{Nm}^{-2}$ (Tuszyński et al., 2005). Theoretical analysis of vibrations in microtubules disclosed radial, torsional, longitudinal, and mixed modes (for instance, radial-longitudinal type is one of the mixed mode). The lowest mode frequencies are in the acoustic range and the highest mode frequencies are of the order of magnitude of tens of gigahertz (Sirenko et al., 1996). Microtubules were analyzed as orthotropic shell structures in (Wang et al., 2006; Qian et al., 2007) and detailed pictures of vibration modes were evaluated.

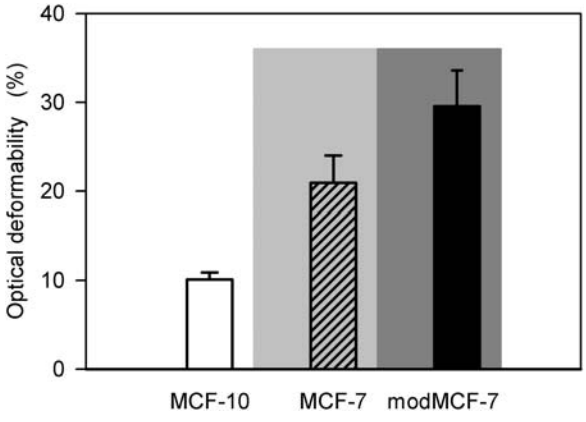


Figure 7. Relative optical deformability of healthy (MCF-10), cancer non metastatic (MCF-7), and TPA modified metastatic cancer (modMCF-7) human breast epithelial cells (adapted from Guck et al., 2005). The grey areas denote disturbed cellular coherent electromagnetic field.

Cancer diagnosis is based on morphological changes of cells caused by disturbed cytoskeleton on the pathway of cancer transformation. Cytoskeleton defects are induced at certain stage of cancer evolution before malignant properties are created. For instance, mechanical stiffness of human epithelial breast cells was investigated (Guck et al., 2005). A stretcher with optically induced forces by two counterpropagating divergent laser beams was used. Deformability of human non tumorigenic epithelial breast cells—MCF-10, of non metastatic cancer (adenocarcinoma) cells—MCF-7, and of modified MCF-7 cells (denoted as modMCF-7) with increased metastatic potential by treatment with TPA (12-*O*-tetradecanoylphorbol-13-acetate) is in Figure 7. Non metastatic cancer MCF-7 and modified modMCF-7 cells exhibit twice and three times greater deformability, respectively, in comparison with healthy MCF-10 cells. The stiffness of the epithelial breast cells displays alterations of the cytoskeleton properties and organization. The grey areas in Figure 7 denote assumed changes of Fröhlich's electromagnetic field.

The relationship between cancer evolution and mechanical properties of cells are analyzed in (Beil et al., 2003; Suresh et al., 2005; Suresh, 2007). Changes of mechanical properties of a cell on its cancer evolution pathway are described in Figure 8. The cytoskeleton defects are characteristic precursors of malignant properties. Investigation of the cytoskeleton and of the mechanical properties of human pancreatic cells (Panc-1) is described. Keratin network in the cell is pathologically reorganized into a ring-like structure around the nucleus within 45 min after application of SPC (sphingosylphosphorylcholine which plays a critical role in the metastatic invasion of gastrointestinal cancers). Keratin structure shrinks and the normalized distance between the outer edge of the keratin structure and the nucleus membrane is reduced to about 50% of the unperturbed value (Figure 9). Deformability of the Panc-1 cells before and after treatment with SPC was measured using the microplate mechanical stretcher method. The relative elastic spring constant decreases to about 40% (Figure 9) and the energy dissipated per one cycle of displacement increases four times after SPC treatment. As a consequence of cytoskeleton disintegration, the endogenous electromagnetic field may be disturbed, which is denoted by grey areas.

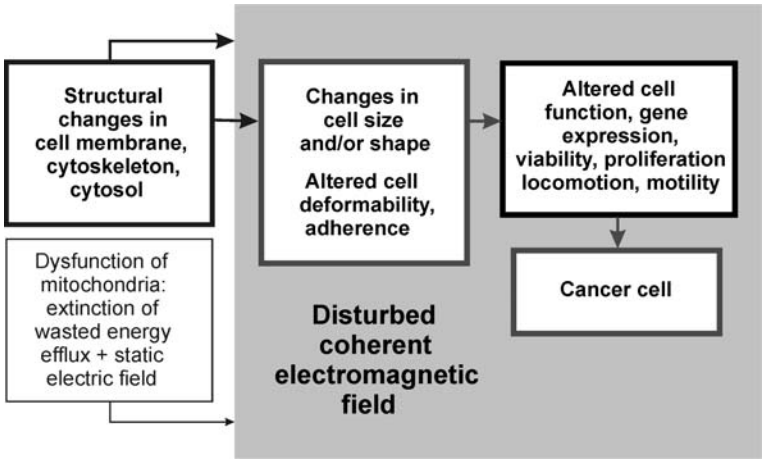


Figure 8. A schematic diagram of mechanical properties of cells on the cancer evolution pathway (adapted from Suresh et al., 2005; Suresh, 2007). Cellular coherent electromagnetic field (grey area) disturbed by cytoskeleton structural defects and/or by mitochondrial dysfunction may be a factor influencing behavior of the cell.

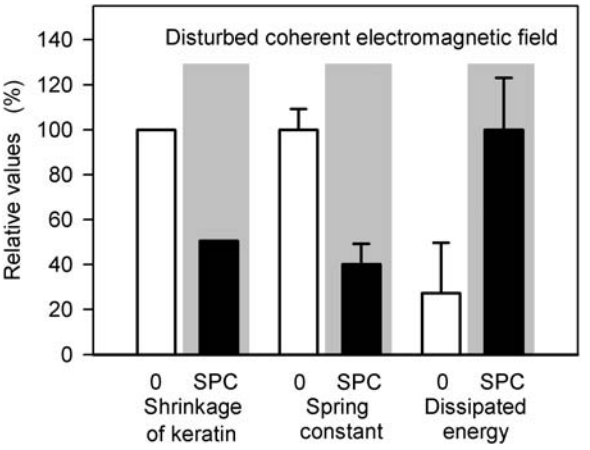


Figure 9. Biomechanical properties of human Panc-1 cancer cells before (the white columns) and after (the black columns) collapse of keratin network caused by SPC treatment (evaluated from data published by Beil et al., 2003; Suresh et al., 2005; Suresh, 2007). Disturbed cellular coherent electromagnetic field (grey areas) may have negative effects on cellular biomechanical properties. (a) The normalized distance between outer edge of the keratin cytoskeleton distribution and the membrane of the nucleus. (b) The relative values of the effective elastic spring constant of the cell measured by mechanical stretcher. (c) The relative energy dissipated per a displacement cycle.

Organization of the mitotic spindle can be disturbed by external electric field with intensity 1–2 V/cm and frequency 100–300 kHz in the M phase of cell cycle as was published in Kirson et al. (2004, 2007) and Cucullo et al. (2005). The forces exerted by the external field on tubulin heterodimers prevent their correct orientation and attraction to the close vicinity of the open tip and, therefore, disturb polymerization of microtubules. The cells (e.g., melanoma cells) are arrested in mitosis by the external field and/or the cells are disintegrated. This effect, i.e., disruption of normal polymerization process, shows biological significance of endogenous electromagnetic fields generated by microtubules.

Malignant Properties of Cancer Cells

Cancer cells at a certain stage of tumor development insinuate themselves into the surrounding tissue, i.e., among the surrounding healthy cells. A sprout burrows a way from the locus of its origin. The profound importance for the cell invasive movements has the cell surface and the surfaces of the surrounding structures with which the cell surface comes into contacts. The invasive motion of the sprout seems

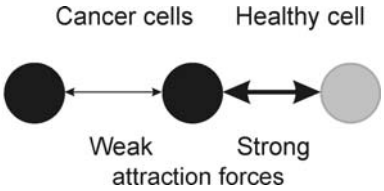


Figure 10. A schematic picture of interaction forces between healthy and cancer cells. Cancer cells may be pulled into a healthy tissue by a force exerted by healthy cells overcoming cancer cells attraction.

to be a result of force effects. We do not discuss here the molecular and biochemical interactions. A hypothetical biophysical model of electromagnetic long range force effects acting between cells is presented (Figure 10 shows possible force effects). Cell as a whole represents electromagnetic vibration system composed of many discrete electric dipoles (Pokorný et al., 1991). If the electromagnetic forces between cancer cells are smaller than forces between healthy cells and cancer cells, then the cancer cells are pulled by healthy cells inside the healthy tissue.

A numerial model supports the assumption. Two Fröhlich's systems mutually interact. The interaction energy I per one system may be expressed by an approximate relation (Pokorný and Wu, 1998):

$$I = \frac{h}{2}\left[\frac{1}{2}\left(\sum_k n_k v_k\right)_{\mathrm{I}} + \frac{1}{2}\left(\sum_\ell n_\ell v_\ell\right)_{\mathrm{I}} - \left(\sum_i n_i v_i\right)_0 - \left(\sum_j n_j v_j\right)_0\right], \tag{6}$$

where v_i, v_j (index 0) and v_k, v_ℓ (index I) are the frequencies of the systems before interaction and in interaction, respectively (n_i, n_j, n_k, and n_ℓ are the corresponding occupation numbers). The frequencies of the interacting systems are given by a simplified relation

$$v^2 = \frac{v_i^2 + v_j^2}{2} \pm \sqrt{\left(\frac{v_i^2 - v_j^2}{2}\right)^2 + (Q^2 v_i v_j)^2}, \tag{7}$$

where Q is the modified interaction coefficient and v represents v_k or v_ℓ.

The force acting between the vibration systems is given by the relation

$$F = -2\frac{\mathrm{d}I}{\mathrm{d}R} = -2\frac{\mathrm{d}I}{\mathrm{d}Q}\frac{\mathrm{d}Q}{\mathrm{d}R}, \tag{8}$$

where R is the distance.

Relations (5)–(8) are used for numerical modeling of Fröhlich's vibration systems and interaction between them.

Figure 11 shows interaction forces between two interacting Fröhlich's systems for $p = 4$ (in Eq. (5)). The p value used determines strong nonlinear dependence of dampinng on excitation. The parameters of the curves are following: C–H curves are evaluated for interaction forces between a system with weak coupling to a heat bath ($\phi_0 = 0.01\,\mathrm{s}^{-1}$) and a system with ϕ_0 given on the abscissa (a "current" value), C–C curves are evaluated for two systems with "current" values of ϕ_0, C–S curves are evaluated for a system with a "current" value of ϕ_0 and a system with high value of ϕ_0 ($\phi_0 = 7.5\,\mathrm{s}^{-1}$, i.e., for the system with strong coupling to the heat bath). The theoretical analysis is based on the assumption that along the pathway of cancer evolution Fröhlich's vibrations are progressively deteriorated by the increase of the linear transition probability ϕ_0, indicating energy losses from the Fröhlich's system (Pokorný and Wu, 1998), by the decrease of energy supply, and by disitegration of the cytoskeleton (causing damage to the system generating the electromagnetic field). Values of ϕ_0 on the horizontal axes in Figure 11 might be also understood as representing a transformed level of phosphorylation. Therefore, the C–H, C–C, and C–S curves determine the interaction forces between a "current" cancer cell and a healthy cell, forces between two "current" cancer cells, and forces between a "current" cancer cell and a cancer cell with strong coupling to the heat bath, respectively.

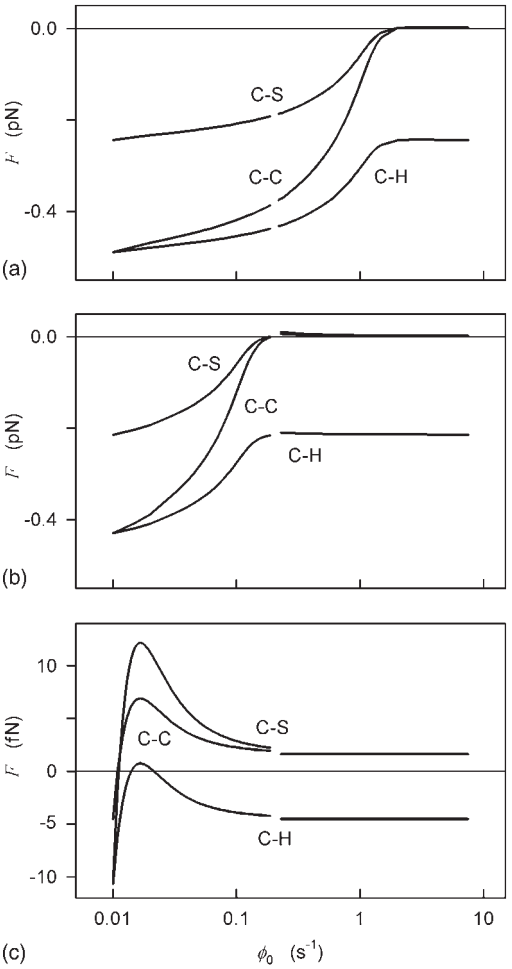


Figure 11. Interaction forces F vs. linear transition probability ϕ_0 between two Fröhlich's vibration systems with the same mode frequencies in the range from 0.1–4 THz, $n_{\max} = 600$, $Q = 0.4$, $\Delta Q/\Delta R = 5 \times 10^6\,\mathrm{m}^{-1}$, $p = 4$. C–H—interaction between a system with ϕ_0 given on the abscissa (a "current" value of ϕ_0) and a system with $\phi_0 = 0.01\,\mathrm{s}^{-1}$. C–C—interaction between two systems with "current" values of ϕ_0. C–S—interaction between a system with a "current" value of ϕ_0 and a system with $\phi_0 = 7.5\,\mathrm{s}^{-1}$. Excitation: (a) $s = 1\,\mathrm{s}^{-1}$; (b) $s = 0.1\,\mathrm{s}^{-1}$; (c) $s = 0.01\,\mathrm{s}^{-1}$. After Pokorný, 2006; Pokorný et al., 2008.

Interaction forces are negative (i.e., attractive) for small values of ϕ_0 and sufficiently high excitation (Figure 11a). If the attractive forces between healthy cells and cancer cells (C–H curves) are considerably greater than the attractive forces between cancer cells (C–C curves), invasion of cancer cells may be a highly probable event. The differences in attraction forces increase along the rising parts of the C–H and C–C curves. The rising parts of the C–H and C–C curves (and, therefore, the region of invasion) are shifted to smaller values of ϕ_0 by decreased energy supply (Figure 11b). For large ϕ_0 values and small energy supply ($s = 0.01\,\mathrm{s}^{-1}$) the forces acting between cancer cells are very small (attractive or repulsive) and cancer cells can mutually detach (Figure 11c). An approximate divide between local invasion and metastatic growth may be delineated at the locus of transition from the rising parts to horizontal flat parts of

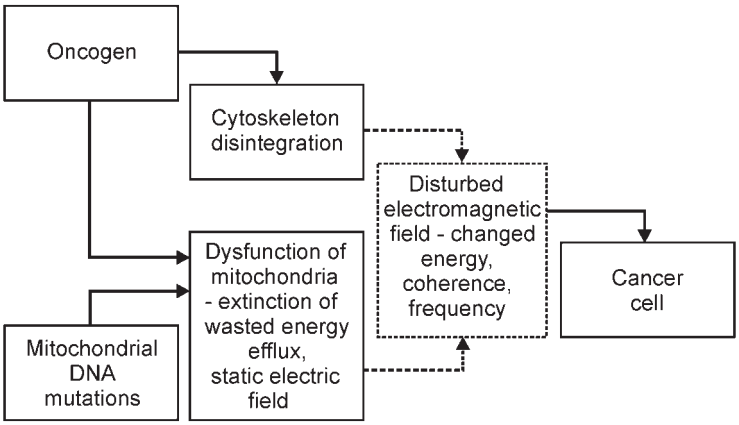


Figure 12. A schematic picture of a hypothetical role of disturbances of coherent electromagnetic field along the cancer transformation pathway. Dysfunction of mitochondria and disorganization of the cytoskeleton can diminish energy level, coherence, change frequency, and the space structure of the electromagnetic field.

the C–H, C–C, and C–S curves. Reduced energy supply to Fröhlich's coherent vibrations can shift the regions of local invasion and of metastasis to smaller values of ϕ_0.

A schematic picture of the cancer transformation pathway which shows the role of mitochondria dysfunction, cytoskeleton disintegration, and of the disturbed coherent electromagnetic field is in Figure 12.

We may conclude that adherence forces between cells determine their behavior: whether cells adhere to or separate from one another. Metastatic nodules are formed in organs which have electromagnetic "similarity" with cancer cells (Pokorný, 2006).

Discussion

Recent research disclosed cytoskeleton disintegration and confirmed significance of mitochondrial dysfunction on the pathway of cancer transformation. Both the pathological events may result in disturbances of Fröhlich's coherent electromagnetic field in cells. Dysfunctional mitochondria may diminish energy supply and nonlinear conditions for energy condensation in microtubules leading to decrease of excitation level and of coherence. Electric polarization of the cytosol is reduced too. Disintegration of the cytoskeleton may have a strong impact on frequency, damping, and on space structure of the generated electromagnetic field. Mitochondrial dysfunction and cytoskeleton disintegration represent different branches of the cancer transformation pathway—their development need not be synchronous and may depend on the type of cancer. The experimental results suggest that mitochondrial dysfunction should precede invasion, and disintegration of the cytoskeleton metastasis (which is shown in Figure 7 by grey and dark grey areas, respectively).

Investigation of electromagnetics links in cancer transformation pathway may disclose new regions that could be effectively targeted by chemical treatment to restore normal cell function (or apoptosis).

Conclusion

Metabolic energy supply to a system with nonlinear interaction between longitudinal elastic and electric polarization fields leads to excitation of coherent vibrations (Fröhlich's

hypothesis). Microtubules in the cytoskeleton satisfy requirements for excitation of coherent vibrations and for generation of a coherent electromagnetic field if mitochondria are functional. The electromagnetic field has organization role in the cell, performs directed transport of mass and charge, and mediates interactions between cells.

Activity of mitochondria is reduced or canceled, oxidative energy production suppressed (Warburg effect), and cytoskeleton disintegrated along the cancer transformation pathway. In cancer cells only about 50% of the energy is supplied by mitochondria. Dysfunctional mitochondrion neither creates a zone of the static electric field nor liberates "wasted energy." Consequently, the cellular electromagnetic field has low energy, disturbed coherence, and changed frequency. Cancer is not only a disease of biochemical processes, but also of biophysical processes, in particular of the biological coherent electromagnetic field. Biological electromagnetic field was measured and its existence proved. Measurement of differences of the electromagnetic field between healthy and cancer cells using microelectronic and nanotechnological systems will crucially contribute to understanding of the cancer process.

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