

FRÖHLICH'S COHERENT VIBRATIONS IN HEALTHY AND CANCER CELLS

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Abstract: Fröhlich formulated the hypothesis of coherent electrical polar oscillations in biological systems. The hypothesis predicts that generated electromagnetic field with a dominant electric component has a basic role in organization, transport, and interactions inside a cell and among cells. If mitochondria are entirely functional, the cellular cytoskeleton satisfies conditions for excitation of coherent states, which are assumed to be essential for normal biological activity. Malfunctioning mitochondria and disintegrated cytoskeleton result in disturbances of the Fröhlich's mechanism and consequently – together with biochemical disturbances – can lead to malignant properties of cancer cells.

Key words: *Biophysical cancer transformation pathway, biological electromagnetic field, coherence, mitochondria dysfunction, microtubules, Fröhlich's hypothesis*

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1. Introduction

For a long time, organization of biological systems was understood as organization of the shape, that is, morphogenesis on the basis of chemical processes. An essentially new concept of organization is based on the role of physical fields in living matter which was formulated by H. Fröhlich. H. Fröhlich postulated the existence of long-range quantum mechanical phase correlations and the existence of vibration modes far from thermal equilibrium and formulated the hypothesis of coherent electrical polar oscillations in biological systems. Fröhlich assumed that nonlinear interactions between elastic and electrical polarization fields with metabolic energy supply result in coherent electrically polar oscillations [1–4].

Organization of biological systems includes three inseparable components: organization of morphological structures; organization of chemical reactions – i.e. of interactions of macromolecules and polymer structures and chains of reactions

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among them; and organization of physical fields, i.e. generation of coherent electromagnetic fields with dominant electric component, essential for organization of the space-time dynamic order [5–7].

In this paper, the possible role of mitochondria and the cellular cytoskeleton in the excitation of Fröhlich's coherent oscillations is described. A pathological state may be caused by disturbances in the mitochondrial function and cytoskeleton structure. Fröhlich conjectured that disturbances of coherent oscillations have a fundamental role in cancer transformation [8].

2. Energy Production in the Cell

Energy production is one of the basic processes in biological systems. Glycolysis and mitochondrial oxidative reactions supply required energy. Pyruvate, the final product of glycolysis, and fatty acids enter the mitochondrial matrix and are broken to acetyl CoA (acetyl coenzyme A), whose energy is used for pumping protons across the inner mitochondrial membrane. A high concentration of protons pumped into the intermembrane space influences the surroundings of the mitochondrion. The outer membrane contains channels permeable to small molecules. Protons diffuse into the cytosol and form a charge layer (Fig. 1) around the mitochondrion. The resulting strong static electric field measurable up to a distance of several μm's is shown in Fig. 2 (a grey zone around the mitochondrion). The intensity of the electric field was measured by fluorescent particles of 30 nm in diameter (shown as small black circular spots in Fig. 2) which are sensitive to electric fields [9]. The intensity of the electric field at the outer membrane is about 3.5 MV/m. As the mitochondrion may occupy about 20% of the cellular volume, the mitochondrial static electric field fills up nearly the whole remaining volume. Consequently, cytosol, cytoskeleton, and biological molecules are electrically polarized.

The electro-chemical proton gradient across the inner mitochondrial membrane drives the production of ATP (adenosine triphosphate). The total efficiency of ATP production is greater than about 40%. The remaining energy (less than about 60%), often denoted as "wasted" energy [10], is liberated from a mitochondrion in the form of heat and photons (Fig. 3). Emission of photons was described, e.g., in [11–12].

The cellular cytoskeleton is assumed to be an oscillating structure generating near-zone electromagnetic fields. The cytoskeleton consists of microfilaments (actin filaments), intermediate filaments, microtubules, and associated proteins. Mitochondria are aligned along microtubules, the main organizer of the cellular cytoskeleton. Microtubule subunits, the tubulin heterodimers, are strong electric dipoles. Theoretical analyses of microtubule mechanical vibrations disclosed that different modes may have frequencies from acoustic up to the GHz region [13–15]. The microtubules seem to be the main structure for Fröhlich's coherent vibrations. The strong static electric field forms conditions for nonlinear oscillations and the "wasted" energy efflux from mitochondria provides energy supply [16–17]. Besides the "wasted" energy liberated from mitochondria, energy is supplied to microtubules from motor proteins moving along microtubules, and from hydrolysis of GTP (guanosine triphosphate) to GDP (guanosine diphosphate) in β tubulin after polymerization. However, the supply of mitochondrial "wasted" energy is very likely to be greatest.

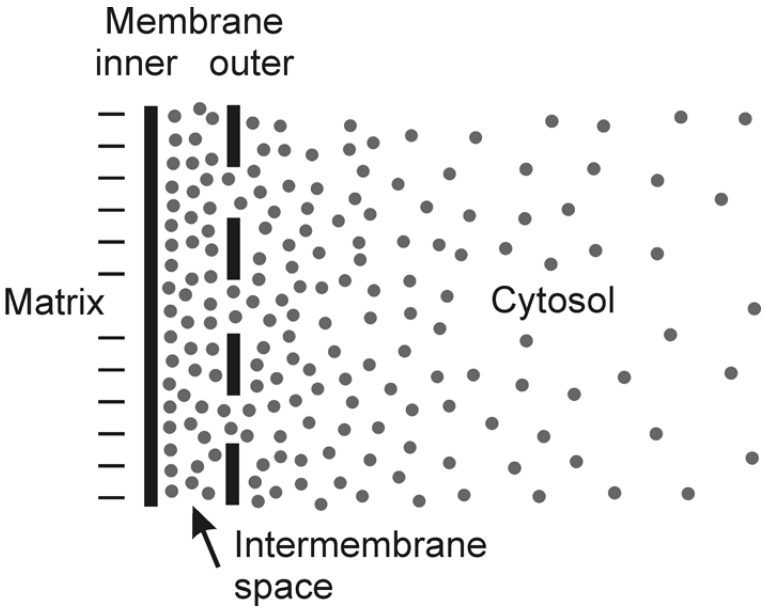


Fig. 1 *Space charge zone around a mitochondrion (protons in the intermembrane space and in the cytosol). The active mitochondrion transports protons across the inner membrane into the intermembrane space.*

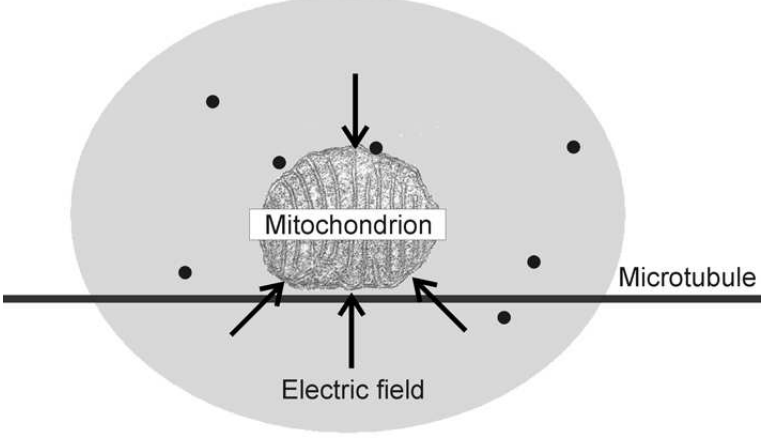


Fig. 2 *A zone of static electric field (the grey area) around a mitochondrion in close vicinity of a microtubule. The intensity of the electric field was measured by fluorescent particles 30 nm in diameter (shown as black circular spots). Intensity of the electric field at the membrane is about 3.5 MV/m (it is very likely the value in the vacuum). The electrical field is measurable up to a distance of several μms from the outer membrane. The arrows denote directions of the intensity of the electric field.*

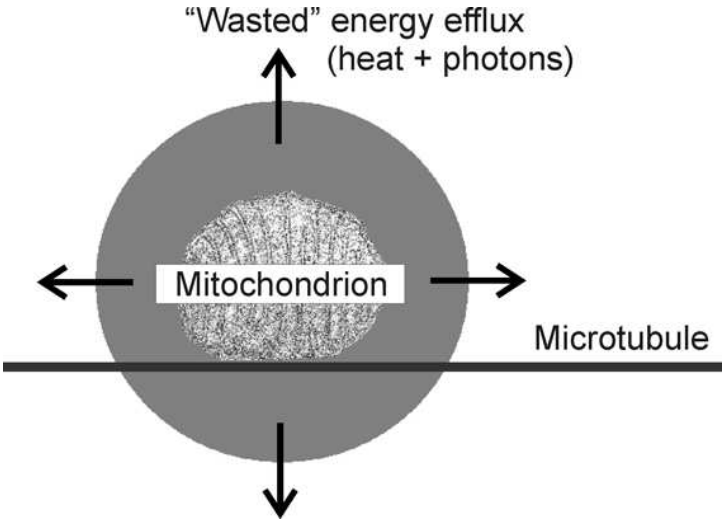


Fig. 3 *Energy which is not utilized for production of ATP is liberated from a mitochondrion in the form of heat and UV (ultraviolet) radiation (nearly 60% of the energy which entered the mitochondrion).*

3. Dysfunction of Mitochondria in Cancer Cells

The oxidative mechanism of ATP production is suppressed in cancer cells and replaced by fermentative production, as was disclosed by [18]. Only about half of the ATP production is supplied from mitochondria [19]. Warburg assumed that this defect has essential influence on cancer cell development and behavior and that "The adenosine triphosphate synthesized by respiration therefore involves more structure than adenosine triphosphate synthesized by fermentation." [19]. Mitochondria dysfunction is also denoted as "the bioenergetic signature of cancer" [20]. Function of mitochondria is suppressed in all types of human cancer that were investigated, for instance in breast, ovarian, colorectal, brain, and others. An overview is, e.g., in [21].

Dysfunction of mitochondria is accompanied by low expression of the K^+ channels, hyperpolarization of the mitochondrial inner membrane, diminution or extinction of the layer of the static electric field around, and by the decrease or interruption of the "wasted" energy efflux. Blockade of normal mitochondrial function in cancer cells is caused by phosphorylation of PDH (pyruvate dehydrogenase) enzyme family (PDH converts pyruvate to acetyl CoA). DCA (dichloracetate) disturbes PDH kinase and reverts mitochondria to the normal function [22]. Functional mitochondria restore the normal cell function or switch on apoptosis of too aberrant cells. Dysfunction of mitochondria very likely gradually evolves in precancerous stages as may be assessed from the cell mediated immunity response to LDH (lactate dehydrogenase) virus antigen during development of precancerous lesions of cervix [23]. LDH virus, a parasite on the cellular energy system, is observed in mitochondria. We may tentatively assume that dysfunction of mitochondria is a key mechanism of malignity in cancerogenesis.

4. Disorganization of the Cytoskeleton

The cytoskeleton is a filamentary structure organizing the cell which participates in cell motility, ribosomal and vesicle transport, mitosis and transduction of pressure and tension. It is composed of actin filaments, intermediate filaments, microtubules, and associated proteins. The cell is in a state of dynamic equilibrium when some filamentary structures contract and other filaments are under pressure [24–25]. Microtubules seem to resist pressure in the cell. Elastic modulus of a cell depends on the state of the cell and changes as a result of internal cellular organization, biochemical conditions, and pathological state.

Tubulin heterodimers, microtubule subunits, are strong electric dipoles. The microtubular structure is nonlinear, and nonlinear properties also depend on the static electric field generated by mitochondria. Energy is supplied to microtubules from hydrolysis of GTP (guanosine triphosphate) in β-tubulin after polymerization, by motor proteins carrying cargo along microtubules, and by absorption of non-utilized ("wasted") energy liberated from mitochondria. Microtubules form a structure satisfying conditions for excitation of Fröhlich's coherent electrical vibrations.

Cytoskeleton defects are induced along the pathway of cancer development before malignant properties are formed [26]. For instance, mechanical deformability of human epithelial breast cells was investigated. Deformation was induced by an optical method using counterpropagating divergent laser beams. Deformabilty of human nontumorigenic epithelial breast cells (MCF-10), of nonmetastatic cancer (adenocarcinoma) cells (MCF-7), and modified MCF-7 cells (modMCF-7) with increased metastatic potential by treatment with TPA (12-*O*-tetradecanoylphorbol-13-acetate) is 10, 20, and 30%, respectively (Fig. 4). Mechanical properties of human pancreatic cells (Panc-1) were investigated and described in [27–29]. The keratin network is pathologically reorganized after the application of SPC (sphingosylphosphorylcholine) which plays a critical role in the metastatic invasion of gastrointestinal cancers. The keratin structure shrinks around the nucleus and the distance between the nuclear membrane and the outer edge of the keratin structure is reduced to about 50% of the unperturbed value (Fig. 5). The relative spring constant decreases to about 40% (Fig. 6a) and energy dissipated per one cycle of measurement increases to about 400% (Fig. 6b) in comparison with the value before application of SPC. Cytoskeleton defects induced along the pathway of cancer transformation result in morphological changes, which are used for histological assessment of cancer development.

The essential biophysical part of cellular processes is shown in Fig 7. The static electric field around mitochondria and "wasted" energy efflux condition excitation of Fröhlich's coherent oscillations in the cytoskeleton and generation of cellular electromagnetic field. The cellular electromagnetic field may be a "tool" for organization, transport, and interactions. Electromagnetic fields of individual organs and of the whole body represent higher hierarchical orders of the field. Biophysical links of cancer transformation pathway include mitochondrial dysfunction [20–21] with reduction or extinction of the "wasted" energy efflux and of the zones of the static electric field. As a result, cytoskeleton oscillations are not sufficiently excited and the energy of the cellular electromagnetic field is low. Along the cancer

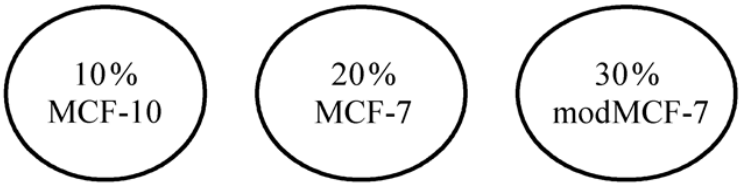


Fig. 4 *Deformability of healthy and cancer cells (the elongation of the ellipses represents schematically deformability of originally circular cells – the shape change corresponds to deformation by the equivalent external forces). MCF-10 – nontumorigenic epithelial breast cells, MCF-7 – nonmetastatic cancer (adenocarcinoma) cells, modMCF-7 – modified MCF-7 cells by treatment with TPA causing an increase of metastatic potential (Biophys. J. – [26]).*

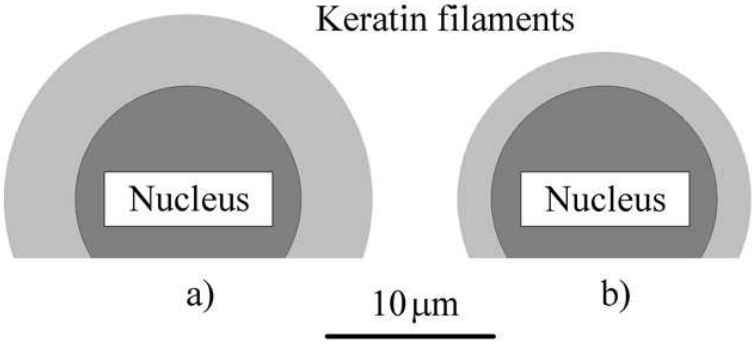


Fig. 5 *A schematic picture of a) keratin network in a Panc-1 cells, and of b) shrunk keratin network in the cells after application of SPC (Nature Cell. Biol. – [27], Acta Biomaterial. – [28], and Acta Material. – [29]).*

transformation pathway, the cytoskeleton is disintegrated, which disturbs the system generating the cellular electromagnetic field. The experimental results suggest that mitochondrial dysfunction should precede invasion and devastating disintegration of the cytoskeleton metastasis. But some cytoskeleton defects evolve before cancer proliferating cells are created as was experimentally proved. This mechanism suggests that the cancer problem cannot be solved without understanding the electromagnetic activity of living cells.

5. Conclusion

The function of mitochondria is not only connected with production of ATP but also with liberation of non-utilized energy and formation of zones of strong static electric field in the cytosol around the outer membrane. Mitochondria are or-

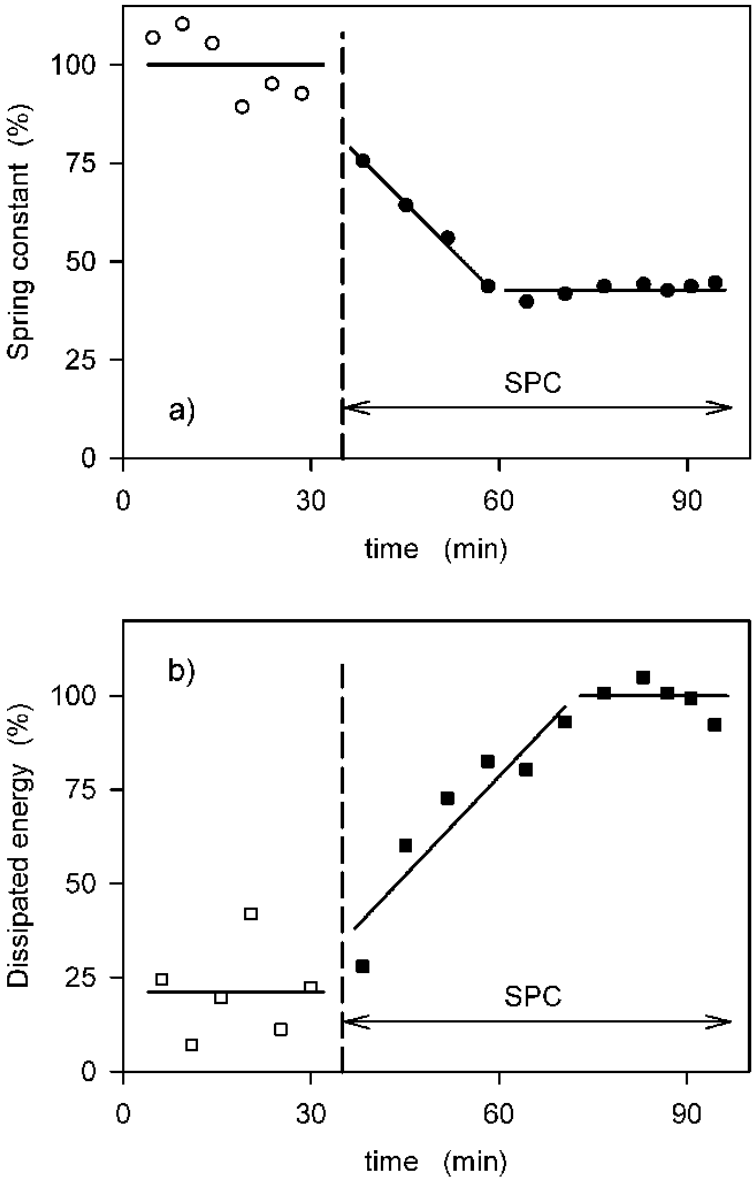


Fig. 6 *Spring constant (a) and dissipated (b) energy of Panc-1 cells measured by a mechanical stretcher before and after application of SPC as a function of time (linear regression lines are evaluated from experimental points). Adapted from data published in [27-29].*

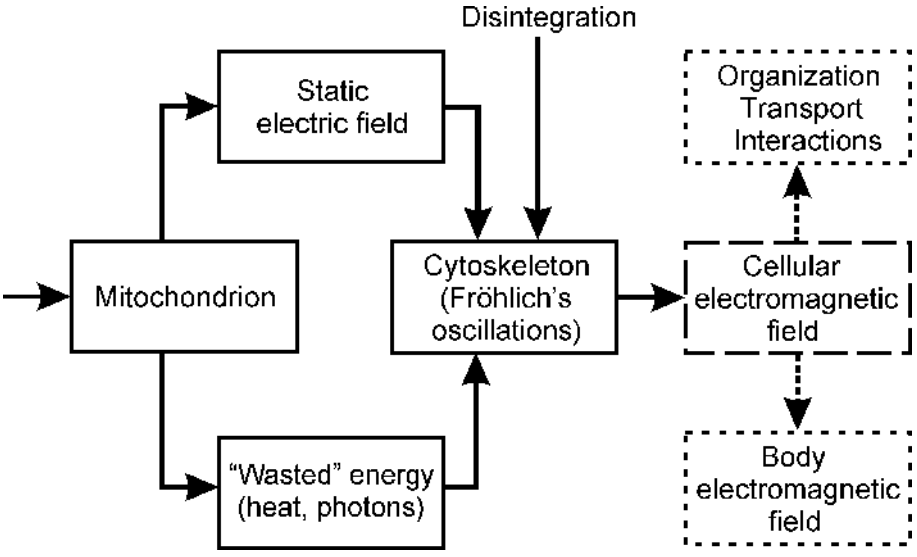


Fig. 7 *A schematic hypothetical picture of the biophysical links in the biological activity of cells. Mitochondria supply energy to the cytoskeleton and create conditions for nonlinear energy transformation from random to coherent. Fröhlich's electrically polar vibrations are excited in the cytoskeleton, which generates coherent electromagnetic field with a dominant electric component. In a cancer cell, mitochondria are dysfunctional and cytoskeleton is disintegrated. The energy of Fröhlich's oscillations and of the generated electromagnetic field is low and coherence is disturbed.*

ganelles which may condition excitation of Fröhlich's coherent oscillations in the cytoskeleton. In a cancer cell, mitochondria are dysfunctional (only about one half of the ATP production comes from mitochondria). Restoration of mitochondria to the normal function converts a cancer cell to a normal cell or switches on apoptosis if the damage of the cell is too extensive. This fact points to a fundamental role of mitochondrial dysfunction in cancer transformation. Deformability of cells increases along the cancer transformation pathway. Devastation of the cytoskeleton structure transforms a nonmetastatic cancer cell into a cell with increased metastatic potential. Biophysical links seem to be crucial in the cancer transformation pathway. We assume that cancer can be effectively treated by restoration of normal coherent electromagnetic activity in cancer cells. Mitochondria seem to be a crucial link for such a treatment.

Abbreviations

ATP – adenosine triphosphate, GTP – guanosine triphosphate, GDP – guanosine diphosphate, PDH – pyruvate dehydrogenase, DCA – dichloracetate, LDH – lactate dehydrogenase (now classified as NAD 1.1.1.27 Oxidoreductase), UV – ultraviolet, TPA – 12-*O*-tetradecanoylphorbol-13-acetate, SPC – sphingosylphosphorylcholine,

MCF-10 – nontumorigenic epithelial breast cells, MCF-7 – nonmetastatic cancer cells, modMCF-7 – modified MCF-7 cells with increased metastatic potential.

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