

Article

Cancer Development and Damped Electromagnetic Activity

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Featured Application: This work brings a framework of fundamental interdisciplinary mechanisms connected with cancer which may promote new methods of diagnostics, prevention, and treatment.

Abstract: Cancer can be initiated in a cell or a fibroblast by the short-circuiting of the cellular electromagnetic field by various fibers, parasitic energy consumption, virus infections, and mitochondrial defects, leading to a damped cellular electromagnetic field. Except short-circuiting (e.g., by asbestos fibers), the central process is mitochondrial dysfunction in cancer cells (the Warburg effect) or in fibroblasts associated with a cancer cell (the reverse Warburg effect), critically lowered respiration, reversed polarity of the ordered water layers around mitochondria emitting electrons, and damped electromagnetic activity of the affected cells. Frequency and power changes of the generated electromagnetic field result in broken communication between cells and possibly in reduced control over chemical reactions, with an increased probability of random genome mutations. An interdisciplinary framework of phenomena related to cancer development is presented, with special attention to the causes and consequences of disturbed cellular electromagnetic activity. Our framework extends the current knowledge on carcinogenesis, to clarify yet unexplained phenomena leading to genome mutation and cancer initiation.

Keywords: mitochondrial dysfunction; damped cellular electromagnetism; energy parasitism; Warburg effect; reverse Warburg effect; disturbed coherence

1. Introduction

Processes related to energy and physical forces play a principal role in the world around us. Energy plays a key role in chemical processes; periodic crystal structures occur due to the presence of attractive and repulsive forces among their building units, etc. Theoretical models are routinely used to characterize known structures and to predict new ones; for example, before an attempt to synthesize a new compound, an energetic model is used to calculate whether the new compound could exist. Unlike nonliving objects in a state of thermodynamic equilibrium, living biological systems are in an excited state that is far from thermodynamic equilibrium [1], maintained by continuous energy supply. To provide an energy supply, living systems perform metabolic activity. In eukaryotic cells, energy in a form of adenosine and guanosine triphosphate (ATP and GTP, respectively) is provided mainly by double-membrane-bound organelles, mitochondria. Chemical energy of ATP

and GTP can be transformed to mechanical, electric, magnetic, or electromagnetic form for biological utilization. Created forces can provide mass transfer, mechanical motion, and ordering of the system itself. Elementary thermodynamic considerations imply that, without the presence of long-range ordering forces, a complex biological system such as a human body would disintegrate within a fraction of a second. It is then obvious that energy-related phenomena in living systems are of even higher importance than in the nonliving world and that the disruption of energetic processes can result in a number of pathologies, including the state of thermodynamic equilibrium called death.

Cancer is an anti-evolutionary process, separating cells from an organized multicellular system, forming their independence, and producing new generations of cells. Connection of the cancer process with disturbed cellular energetics was first described by O. Warburg [2,3]. Cancer process is a pathology connected with mitochondrial dysfunction—reduced oxidative metabolism in mitochondria to about 50% due to suspension of the oxidative processing of pyruvate (Warburg effect). Missing energy is replaced by fermentative decomposition of glucose in the cellular volume, which is a similar process by which, e.g., muscle cells use an additional energy source in case of increased physical exertion. Warburg assessed differences of the ordered and disordered cells of the embryos and of the tumors, respectively, with a conclusion that “The adenosine triphosphate synthesized by respiration therefore involves more structure than adenosine triphosphate synthesized by fermentation”. However, disturbance of the oxidative energy production has been accepted by the general biological scientific community as a negligible side effect of cancer development, even after its explanation by mitochondrial dysfunction. The origin, nature, and essence of the organization forces and energy transformation mechanisms for their excitation were generally neglected for a long time, regardless of widely used cancer diagnostic methods of cytology and histology, showing a strong disorder in cancer cells. It is well-known that disorder can be a consequence of weakened ordering forces or of an effect of strong random activity which overcomes the ordering measures (or a combination of both cases).

Chemical bonds (covalent, ionic, hydrogen, and Van der Waals) have been supposed to be a primary phenomenon to drive ordering and activities in biological systems. However, chemical bonds are connected with short-range forces acting at nanometric distances, while biological systems exhibit ordering at all length scales [4,5]. Centrally organized systems need at least ordering forces, communication, and information processing; biological systems are not excluded. For example, thousands of chemical reactions can occur simultaneously in a cell. At a given moment, only some of them are prevailing, followed by others, etc. A sophisticated control over a large scale is obviously in action which cannot be provided by neighbor-to-neighbor effects, such as diffusion, or by purely chemical agents. Of the known mechanisms, such a control can be provided by electric or electromagnetic field. Electric field can provide dielectrophoresis (polarization and motion of charged particles), attraction or repulsion of charged particles, shift of resonant frequencies, and increase or decrease of energy. Oscillating electric field may excite oscillations in microparticles and structures, and in the case of resonance (equal frequencies of the field and of the structure), the acting forces are strong. Electric or electromagnetic field being the only known phenomenon providing fast interaction and strong enough forces at all length scales, an idea was introduced of ordering and control by electromagnetic field generated by the living structures themselves.

A theoretical background based on a hypothesis of coherent electrical polar vibrational states was given by H. Fröhlich [6,7]. Coherent electromagnetic activity in a wide spectral region, from acoustic frequencies to the UV region, can be considered a fundamental expression of life [5]. In multicellular systems, an electromagnetic field is supposed to be generated by microtubules with a periodic structure of tubulin heterodimers and oscillating electric dipoles [8]. At nanometric scales, the near component of the electric field is supposed to reach extremely high values [9]. Such an intense field can excite valence electrons to energies comparable with energy of chemical bonds. In such a configuration, biochemical reactions might be controlled by the oscillating field providing selectivity of bonds [9].

The presence of an electromagnetic field can be visualized by its force effect on polarized and charged particles and structures—their motion, changed distribution, oscillation, etc. The biological

electromagnetic field has been experimentally proved by Pohl et al. [10], Hölzel [11], Pokorný et al. [12], and Sahu et al. [13]; its amplitude increases in important processes requiring energy supply, such as cellular division (M phase). An experimental study of enzymatic reactions and their acceleration by a factor up to 10^5 in a strong electric field [14] led to a conclusion that the electric-field-dependent acceleration of elementary reactions might be a general concept in biological and chemical catalysis [15]. Both theoretical predictions and experimental data thus indicate that decreased power of the generated field due to the dysfunction of energy-providing mitochondria can lead to a replacement of controlled biochemical reactions by random chemical processes [9]. On the other hand, routinely observed disturbed ordering in cancer cells is clear evidence of changed organization forces, regardless of the mechanism of their generation.

The lifetime risk of cancers of many different types is strongly correlated with the total number of divisions of the normal self-renewing cells maintaining the tissue homeostasis [16]. Therefore, the total probability of cancer initiation depends on the sum of individual probabilities of division, particularly in the periods of stem cells. Cancer transformation is assumed to be caused by an oncogene mutation [17–22]. Nevertheless, understanding the origin of the genome somatic mutation is rather limited. Thousands of somatic mutations (passengers) are accompanying the oncogene mutation (driver) in a single cancer sample [17]. The experimental results very likely demonstrate a disturbed protection of selectivity of chemical reactions and their randomization in cancer cells which may involve genome mutations.

The pathway of chemical bonding to the genome and transferring consequences of the oncogene mutation involves a sequence of processes, each of which faces major obstacles. Access to DNA is heavily restricted, e.g., by supercoiling, limiting full access to the cell-division period. Random mutations can be corrected by DNA repair processes. If a specific oncogene mutation occurs, the oncogene expression toward mitochondrial dysfunction meets another obstacle: the cell mobilizes tumor-suppressor networks to avert the hazard of malignant transformation and to be withdrawn from the proliferative pool. One of the mechanisms, oncogene-induced apoptosis, triggers a preprogrammed death of a cell suffering from large enough DNA damage. Oncogene-induced senescence (OIS) represents a complementary mechanism depending on the response to induction of DNA damage [23]. OIS is induced by suppression of the PDH kinase and induction of PDH phosphatase, resulting in increased respiration [24]. Mitochondrial dysfunction is an effector pathway of OIS [25]. Even if tumor-suppressor networks become inactive, the tumor-suppressor genes can be reactivated [26]. All the processes leading to cancer transformation of the cell must occur during a limited timescale of the cellular life cycle. The resulting cancer cell must then evade the supervision of the cell-mediated immunity (CMI) response involving T-lymphocytes (part CD₄Ly). A specific oncogene mutation and/or overexpression, together with the loss of tumor suppressors, is a complex process which should occur simultaneously in a large enough number of cells to initiate cancer. It is therefore reasonable to assume that a production of mitochondrial dysfunction by an isolated oncogene mutation without other serious pathologies has a low probability.

Oncogenic viruses play a special role as experimental models for investigating cellular networks [27]. A number of viruses associated with human cancer have been identified, e.g., Epstein–Barr virus, hepatitis B and C viruses, human herpes virus 8, human T-cell leukemia virus, and HIV-1. More than 170 individual types of human papillomaviruses (HPV) have been classified [28–31]. Despite their different nature related to different virus families, oncogenic viruses share key features, in particular, prolonged latency and their ability to establish long-term persistent infections instead of killing their host cells [27]. To achieve that, they must employ strategies for evading immune response of the host. A long-term interaction between a virus and its host seems to be an important factor for cancer development. Cancer is assumed to be initiated when a viral coding sequence is integrated into oncogene of the cellular genome as a result of infection. Carcinogenicity of oncogenic viruses may be connected with their capability to disturb or overcome protection of biochemical genome bonding. Besides that, a virus as a living system requires energy to be supplied from the host cell.

A reduced energy supply utilized by the cell inevitably causes lowered amplitude of the generated electromagnetic field, lowered organization forces, and possibly—at some critical stage—disturbed write protection of the DNA [9]. About 15–20% of all human cancers are estimated to be caused by viral infections [27]; however, the role of viruses is supposed to be underappreciated [32]. In contrast to many other carcinogenic agents, they provide a direct mechanism contributing to cancer initiation (writing into DNA of the host cell), together with indirect ones (inflammation or other chronic effects). Nevertheless, the probability of such a process depends on the virus activity and cellular protection levels. It has to be admitted that the actual occurrence of cancers caused by viruses might be higher than the so far estimated figure, e.g., if further oncogenic viruses are revealed.

We suggest that disturbances of the energy levels possibly resulting in serious pathologies might be caused by energy-consuming parasites, such as the lactate dehydrogenase (LDH) virus (or Riley virus, now classified as NAD 1.1.1.27 Oxidoreductase). Our extensive immunological study [33–37] revealed a response to the LDH virus antigen in (statistically) all cancer patients. However, establishing etiological role of a pathogen in chronic diseases with decades-lasting incubation period is difficult. A possible approach by Yerushalmy and Palmer [38] involves proving (A) the simultaneous presence of the organism and disease and their appearance in the correct sequence, and (B) the specificity of effect of the organism on the development of the disease. We discuss the postulate (A) in terms of our experimental data and (B) by explanation of carcinogenesis, by suggesting a biophysical model, based on published experimental data to a significant extent. Our model extends currently acknowledged theories on cancer initiation primarily by providing explanation of the processes preceding the oncogene mutation.

2. Materials and Methods

Cell-mediated immunity (CMI) response is considered to correlate with adherence of T lymphocytes to some solid-state surfaces [39] and interaction forces between human CD₄Ly cells with the antigen [40]. Leukocyte adherence inhibition (LAI) assay is based on microscopic evaluation of in vitro adherence of T lymphocytes to surfaces of specific glass or plastic materials in the presence and in the absence of antigens. Two types of antigens were used. The specific antigen is an immunological functional fraction prepared from a malignant tumor of the same type as the malignancy of the patient from which the blood was taken. The nonspecific antigen is an immunological functional fraction prepared from the serum of inbred laboratory mouse C3H H2k strain infected with the LDH virus. Both antigens prepared by high-pressure gel chromatography are ribonucleic acids (RNA). A comprehensive description of the experimental method including preparation of T lymphocytes and the antigens is available in [9,33,34,37]. Sorption effects for separation of a complex naturally occurring mixture of high-molecular-weight compounds is described in Vytášek et al. [41]. A simple and sensitive test for detection of tumor-specific antigen mediated by macrophage adherence inhibition is in Holář et al. [42]. The gel chromatogram of antigen fractions prepared from human carcinoma and inbred mice (strain C3H) infected with LDH virus is in Jandová et al. [37]. Besides chemical reactions, the antigen was separated by a differential refractometer and a spectrophotometric detector, and the data were recorded, using a two-channel Philips PM 8010 recorder [43]. The antigen is a 340 nm fraction. A schematic picture with the receptor, ligand, and signaling pathway is in Jandová et al. [36].

The CMI response by the described method was investigated on patients with cancer of the cervix, endometrium, ovary, breast, and lung, as well as melanoblastoma and otorhinolaryngological cancers. Cancer diagnosis was verified by histopathology, using cell samples taken during surgery. Conditions for malignant transition in cancer development were studied on precancerous cervical lesions. These lesions were diagnosed by cytological (PAP) smears, from examination by colposcopy and from colposcopically directed ‘punch’ biopsy material by histology. The grades of development of precancerous lesions LSIL and HSIL (low- and high-grade squamous intraepithelial lesions, respectively) were determined by cytology, and CIN 1, 2, and 3 (cervical intraepithelial neoplasia) grades by histology—Jandová et al. [37].

Cells from healthy humans adhere both without and with the antigens, adherence of cancer cells with both antigens is decreased, and the mutual difference is small. The results of LAI assay were evaluated in three regions—healthy, noise, and pathological (e.g., cancer). A relative number is used: $M = 100 \cdot m/m_0$ (in %) where m_0 and m are numbers of cells in the suspension before and after the sedimentation–adhesion process is used.

The LAI assay is a complex and tedious experimental method, and unequivocal results are conditioned by a high purity of antigens. Chemical and physical agents can affect the cell-mediated immunity response [34–36]. For example, magnetic field 0.5–10 mT decreases (increases) adherence of CD₄Ly taken from healthy humans (cancer patients). Magnetic field can affect adherence surface of glass, interaction forces between CD₄Ly, and properties of antigen, but the mechanism of such behavior is unknown.

A positive response to the nonspecific antigen was also examined in patients with acute myocardial infarction, schizophrenia, and recurrent spontaneous abortions in early pregnancy from unknown reasons [44].

3. Results

3.1. Warburg Effect (Differentiated) Cancers

Energy transport, processing, and parceling out into small bits stored in ATP and GTP form a joint fermentative and oxidative pathway crucial for life. Warburg disclosed that healthy tissues produce the majority of energy by respiration, while cancer tissues produce approximately the same amount of energy by fermentation as by respiration, i.e., about 50% by metabolizing glucose to lactic acid 2,3. Transport of pyruvate, a product of glycolysis, to mitochondrial matrix is decreased by dysfunctional pyruvate dehydrogenase (PDH) enzymes, and this deviation is called a mitochondrial dysfunction or the Warburg effect.

Mitochondrial function is connected with a transfer of hydrogen (H^+) ions across its inner membrane and a formation of a charged layer of H^+ ions in cytosol around mitochondria. Due to the H^+ transfer, pH values in matrix and cytosol change. H^+ ions transferred to the cytosol form a layer creating an electric potential across the inner membrane. Further in the text, we denote this electric potential as *actual* potential, and it should be approximately proportional to the number of H^+ ions transferred to the cytosol, which is in turn related to the amount of the energy produced by oxidative processes. The actual electric potential of the fully functional mitochondria evaluated from the transfer of H^+ ions is about −140 mV, and that of the dysfunctional mitochondria about −70 mV [45]. These values contrast to the *apparent* potential values of −100 and −160 mV, respectively, measured by uptake and retention of positively charged fluorescent dyes, such as Rhodamine 123 [46]. The differences can be explained by the presence of an additional potential layer of ordered water formed in the region of the high-intensity electric field of the H^+ ion layer [47].

Water ordering in regions of a high electric field is a general phenomenon [48]. Ordered water layers up to 0.5 mm thick are formed in areas of a large gradient of the electric potential and at charged surfaces, regardless of their chemical composition. Ordered water layers can be formed at a plasma membrane, at the layer of H^+ ions around mitochondria, and at charged surfaces of macromolecules. A theoretical model describes water ordering in terms of electronic excitation, i.e., coherent oscillations and vortexing of electrons in molecules [49,50]. Electrons in water molecules are supposed to coherently oscillate between a fundamental state with strongly bound electrons (where the energy to expel an electron amounts to 12.60 eV) and the excited state with weakly bound electrons (where the expel energy is about 0.54 eV). Therefore, an ordered water layer can be a donor of electrons. The thickness of the ordered water layer depends on the pH value: it increases with increasing offset from an *intermediate point*, pH_0 , where the ordered water layer is not formed [48]. For $pH < pH_0$, the intensity of the electric field in the ordered water layer is oriented in the opposite direction from that in the H^+ layer forming the actual potential of mitochondria (Figure 1), and positively charged particles are excluded from

the layer. For $\text{pH} > \text{pH}_0$, both intensities of the electric field are oriented in the same direction, and negatively charged particles are excluded.

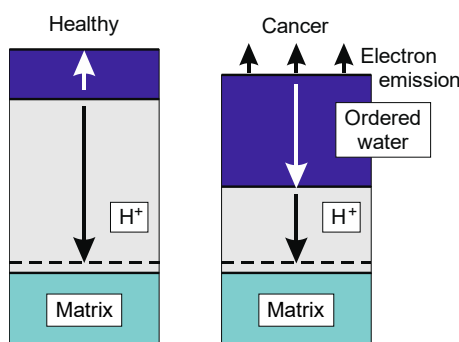


Figure 1. Potential layers at the inner mitochondrial membrane of functional (Healthy) and dysfunctional (Cancer) mitochondria. The electric potential consists of two components—the actual electric potential of the electrochemical H^+ gradient and the potential of the ordered water layer. The vertical dimensions of the layers correspond to the electric potentials and the inner arrows denote orientations of the intensity of the electric field. For $\text{pH} < \text{pH}_0$, the intensity of the electric field in the ordered water layer has an opposite direction to the electric potential of the electrochemical H^+ gradient. For $\text{pH} > \text{pH}_0$, both directions are the same. The intermediate value pH_0 determines the point where the ordered water layer is not formed. The arrows at the upper surface of ordered water layer in the cancer case denote emission of electrons which damp the electromagnetic field.

The thickness and the properties of the ordered water layer at the mitochondrial membrane depend on the difference of the electric field generated by H^+ layer and by the surrounding cytosol (dependent on pH), and on the difference of proton concentration (forming the electrochemical proton gradient which exerts a proton motive force). Cytosol may have pH about 7.2 (neutral medium). However, cells are able to control the pH of their intracellular compartments (e.g., even 5 pH). Inside mitochondria pH is higher than 7.2. The mitochondrial proton layer may correspond to a difference of about -1 pH . The measured values of the potentials and dependence of the thickness of the ordered layer on pH make possible to prepare an approximate model of the mutual position of the healthy and cancer cells on pH and forming of ordered water layers with different polarization. In the model, a healthy cell has the intermediate point about 6 pH and the cancer cell higher—Pokorny et al. [47]. It should be noted that this is only a crude approximation, as the pH processes inside cells depend on many physical and chemical factors in cytosol and inside mitochondria, as well as on biological activity.

The potential across the ordered water layer at the mitochondrial membrane can be obtained as a difference of the apparent minus actual electric potentials for functional and dysfunctional mitochondria. Dependence of the intensity of the electric field in the ordered water layer on pH can affect electromagnetic activity in cells [51]. For $\text{pH} > \text{pH}_0$, the ordered water has a high tendency to release electrons [49]. The electrons are transported into cytosol and form a conductive environment which can strongly damp the electromagnetic activity of the cell [47,52–55].

Cellular oscillating systems are strongly nonlinear [56]. Resonant frequency of such a system is not a constant; it depends on the energy stored in the oscillating system. Changed amplitudes of cellular oscillations due to their damping result in frequency shifts to higher values compared to those in the healthy state. The interference pattern of the electromagnetic field is then rebuilt and shifted, resulting in disturbed organization forces. Due to different oscillation frequencies in healthy and cancer cells, their mutual electromagnetic communication must be disrupted at least to some extent. Disturbed electromagnetic activity, a fundamental feature of all cancers [57], thus can enable a cancer cell to liberate itself from the tissue.

A strong-enough electric field can heavily influence chemical reactions, e.g., enzymatic reaction rate can be enhanced up to 10^5 -fold by the presence of a static electric field [14]. Resonant effects

of oscillating fields can be even many orders of magnitude stronger. Photon absorption can modify the electronic configuration of an atom or molecule and thus enable chemical reactions which would otherwise be impossible. By varying the oscillation field, chemical reactions might be efficiently switched on and off by a suggested mechanism of the *reverse vibrational Stark effect* [9], particularly when the photon energy absorbed by a valence electron is higher than the energy of chemical bonds (van der Waals attraction to covalent bonding correspond to a photon frequency range of 10^{12} – 10^{17} Hz). It is reasonable to assume the mechanism to be involved in controlling information storage into DNA. We suggest that if the oscillating field is damped, selective reactions might be replaced by standard chemical reactions which may then lead to a number of random writings into DNA, causing massive genomic mutations.

Similar effects can be caused by short-circuiting of the cellular generating structures by nanofibers or other structures which have penetrated into the cell. Asbestos filaments are the most discussed structure of the type. The filaments represent optical fibers or conducting wires that provide a short-circuit for the cellular electric and/or electromagnetic signals [58,59]. Both pathological mechanisms, i.e., damping and short-circuiting, are fundamental processes resulting in cancer. Decreased power, disturbed coherence, and changed frequencies are conditions for disturbed order inside the cell and the tissue, local invasion, and metastases. Gradual evolution of the pathological processes corresponds to gradual morphological changes routinely observed.

3.2. Reverse Warburg Effect (Undifferentiated) Cancers

The reverse Warburg effect [60] is a tissue process of a pathological cooperation between a cancer cell and associated fibroblasts. Pathological processes in inflicted fibroblasts associated with the cancer cell are similar to those in the Warburg effect cancer cells. Pathological transformation of the fibroblast is controlled by signaling from the tissue and from the cancer cell. Loss of stromal Caveoline-1 (Cav-1) expression results in increased production of nitric oxide, enlarged reactive oxygen species (ROS) production, increased oxidative stress, and mitochondrial dysfunction in fibroblasts. By altered model for tumor–stroma co-evolution, cancer cells induce oxidative stress in adjacent fibroblasts and possibly in other stroma cells. Oxidative stress in the tumor stroma mimics the effect of hypoxia under aerobic condition and produces other processes for cancer development Lisanti et al. [61]. Excess stromal production of reactive oxygen species is assumed to be a basis for the following chemical reactions, but energy processes caused by increased damping are not assumed.

The cancer cell is fueled by energy-rich metabolites, such as lactate, pyruvate, glutamine, and ketone BHB (beta-hydroxybutyrate), produced by the stroma cells. Their high energy supply leads to a high excitation of the generated electromagnetic field. The reverse Warburg effect cancer cells are shifted to an unstable highly nonlinear region, their working point may float with energy supply, and coherence is disturbed. Their electromagnetic forces are strong but with varying amplitudes. Oscillation frequencies are lower than those in the healthy state and fluctuating. Due to strong but unstable acting forces, the morphological changes are pronounced so that the cancer cells do not resemble their original counterparts. Advanced prostate cancers, for example, can transform to this phenotype [60].

3.3. LDH Virus—An Energy Parasite

In 1960, V. Riley discovered LDH virus (lactate dehydrogenase elevating virus or Riley virus), an agent that systematically affects experimental results in cancer research on mice [62]. It can be transferred primarily by blood, including direct transfer from a mother to offspring. After approximately a week of lasting acute infection, the virus reduces to its ribonucleic acid (RNA) chain, covered with a structure similar to the membrane of the host cell, which helps in evading detection by the immune system. A lifelong chronic infection follows. The virus is considered a perfect parasite [63–65]—the gradually growing population of RNA chains causes no apparent harm to the host cell, and no morphological changes or obvious disease occur. The RNA chains “only” parasite on cellular energy resources,

particularly ATP. In infected cells, the level of LDH enzyme is elevated five- to ten-fold, compared to noninfected cells. The LDH enzyme catalyzes a conversion of reduced NADH (nicotinamide adenine dinucleotide + hydride ion H^-) to oxidized NAD^+ and vice versa [63]. Pyruvate, the final product of glycolysis, is converted to lactate before it can be transferred to mitochondria, which forms a parallel pathway to inhibition of pyruvate transfer to mitochondria by dysfunctional PDH (Figure 2) in Warburg effect cancer cells. The infected cell with a population of viral RNAs exceeding some critical level then behaves in a similar way as a Warburg effect cancer cell, or dies as in the case of heart infarction. A possible connection of the LDH virus with cancer was studied by Rowson and Mahy, and Riley and Wroblewski [63,66]; changes of the immune activity in the acute phase of the LDH virus infection are given in [67]. Cell-mediated immunity (CMI) response to the LDH virus antigen, extensively studied by Jandová et al. [33–37], indicates activity of the LDH virus or a similar pathogen in humans.

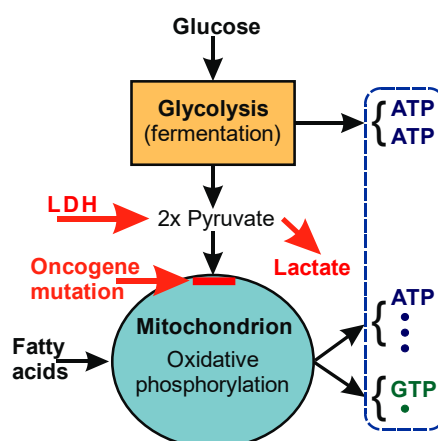


Figure 2. Energy transformation by glycolysis and oxidative phosphorylation in living cells. Cancer development can result from inhibition of pyruvate transfer to mitochondrial matrix. Parasitic energy consumption and transfer of pyruvate to lactate form a parallel pathway to mitochondrial dysfunction caused by deactivated PDH enzymes.

3.4. Immune Response Study

The immune system is one of the most complex structures in a human body. It responds to a presence of antigens, i.e., molecules or molecular fragments characterizing individual pathogens. The presence of antigens is detected either directly or indirectly through antibodies. There are two main mechanisms of immunity—humoral and cellular. The latter is mediated by T lymphocytes. Since the 1960s, a group of Czech scientists studied cell-mediated immunity (CMI) of healthy blood donors and patients with various tumors. The study was focused on the immune response of cytotoxic T-lymphocytes, leukocytes capable of killing whole cells, such as bacteria, cells infected by viruses, cancer cells, etc. Pathogenic cells are directly detected by receptors on the cellular membrane of a T lymphocyte. Quantitative assessment can be based on the fact that the cell-mediated immune response by T lymphocytes correlates with their adherence to appropriate glass or plastic surface. The method is referred to as leukocyte adherence inhibition (LAI) test.

The LAI method was used to study CMI response on over 12,000 patients with cancer of the cervix, endometrium, ovary, breast, and lung, as well as melanoblastoma and otorhinolaryngological cancers [9,33–37]. T cells were separated from venous blood, and three sample solutions for microscopic evaluation of non-adhering cells were prepared: (1) a solution containing T cells only; (2) a solution of T cells with a specific antigen, i.e., immunological functional fraction prepared from tumors of the same type as the tumor found in the patient; (3) a solution of T cells with a nonspecific antigen, i.e., immunological functional fraction obtained from the serum of inbred laboratory mouse strain C3H infected with the LDH virus. T cells of healthy blood donors did not show a significant response to the presence of the antigens. On the contrary, the presence of both antigens elicited a strong response for

the vast majority of cancer patients. It should be noted that the specific antigen elicited a response only for patients with tumors corresponding to the specific antigen obtained from a tumor of the same type, while the nonspecific antigen of the LDH virus elicited a response for all cancer patients. Healthy T cells (cancer cells) with antigen exhibited the relative number $M = 96.68\%$ (0.6%), 2.65% (2.05%), and 0.67% (97.35%) in healthy, noise, and pathological regions, respectively.

The LAI method was also applied to patients with various grades of development of precancerous cervical lesions. The experiment revealed 27.7% and 34.8% of the cases corresponding to healthy women for specific and nonspecific antigen, respectively, and 67.0% and 59.8% corresponding to patients with tumor. No statistically significant difference was revealed for different grades of lesion development, which corresponds to the fact that behavior of precancerous events is unpredictable and invasive carcinoma may develop from any level of precancerous abnormalities [68]. The results indicate that the precancerous stage is a critical phase of cancer transformation of a cell.

3.5. Morphology of Healthy and Cancer Cells

Evaluation of morphological pictures of tissues, cells, nuclei, nucleoli, membranes, and chromatin belongs to standard diagnostic methods for cancer. Histological and cytological pictures are routinely used. Morphological changes and their evolution serve as significant criteria of cancer development. The Warburg effect (differentiated) cancer cells resemble their original cells, and their morphological changes develop gradually. The final stage of their development is indicated by local invasion and metastases. Their behavior is predictable. A comprehensive assessment of their slow gradual development seems to be a sign of increasingly disturbed and weak organization forces. The reverse Warburg effect (undifferentiated) cancer cells do not resemble their original counterparts. They are small, with large nuclei, scant cytoplasm, and foci of necrosis. The most startling properties are their violent growth, aggressiveness, and early invasion in surroundings and metastases, which indicates strong forces in a disordered system.

Development of the Warburg effect (differentiated) cancers is shown in Figure 3:

- **Figure 3A** displays normal squamous cells from uterine cervical surface area of a healthy woman. Cytoplasm is abundant and has distinct borders. The nuclear–cytoplasmic volume ratio is in favor of cytoplasm and can be about 5/60. **Possible physical view:** This picture shows a healthy state. The pathological development is hidden as long as the decrease of the oxidative energy production does not result in damping of power of cellular electromagnetic field, organization forces in the cell remain unchanged, and oncogenes not transformed. It should be emphasized that a considerable part of the development of the Warburg effect is not visible by itself.
- **Figure 3B** shows cells of low-grade squamous intraepithelial cervical cell lesions which have enlarged nuclei of about three times with respect to a healthy cell and well-defined cytoplasm. **Possible physical view:** The power of the electromagnetic field in the cell is lowered, and the most sensitive organization activities are disturbed, but the oscillation frequency seems to coincide with healthy cells. The power in the cell could be kept at a considerably high level by an energy supply from neighboring cells connected through tubulin nanotubes.
- **Figure 3C** displays cells of high-grade squamous intraepithelial cervical cell lesions with variable size of cells, variable size and shape of nuclei, quite irregular nuclear membrane, and reduced cytoplasm. The degree of nuclei enlargement is more variable than that in the low-grade case. **Possible physical view:** Connections by tubulin nanotubes between cells are disturbed and electromagnetic power is low. The power and frequency of oscillations differ between healthy and cancer cells, and between cancer cells. Cancer cells are not selectively interacting with healthy cells in the tissue and become independent entities.
- **Figure 3D:** Marked pleomorphism of cellular size and shape as a characteristic property of invasive squamous cell cancer can be recognized. Cell borders are poorly defined, cytoplasm is missing, size and shape of nuclei manifest large differences, and chromatin in nuclei is coarsely clumped. Debris of cells and vessels can be seen in the background. **Possible physical view:** The power of

the electromagnetic field in cancer cells is very low, and its level in similar cancer cells is different. Variation of frequency resulted in repulsion forces between cancer and healthy cells. Power and frequency of oscillations have strong random components.

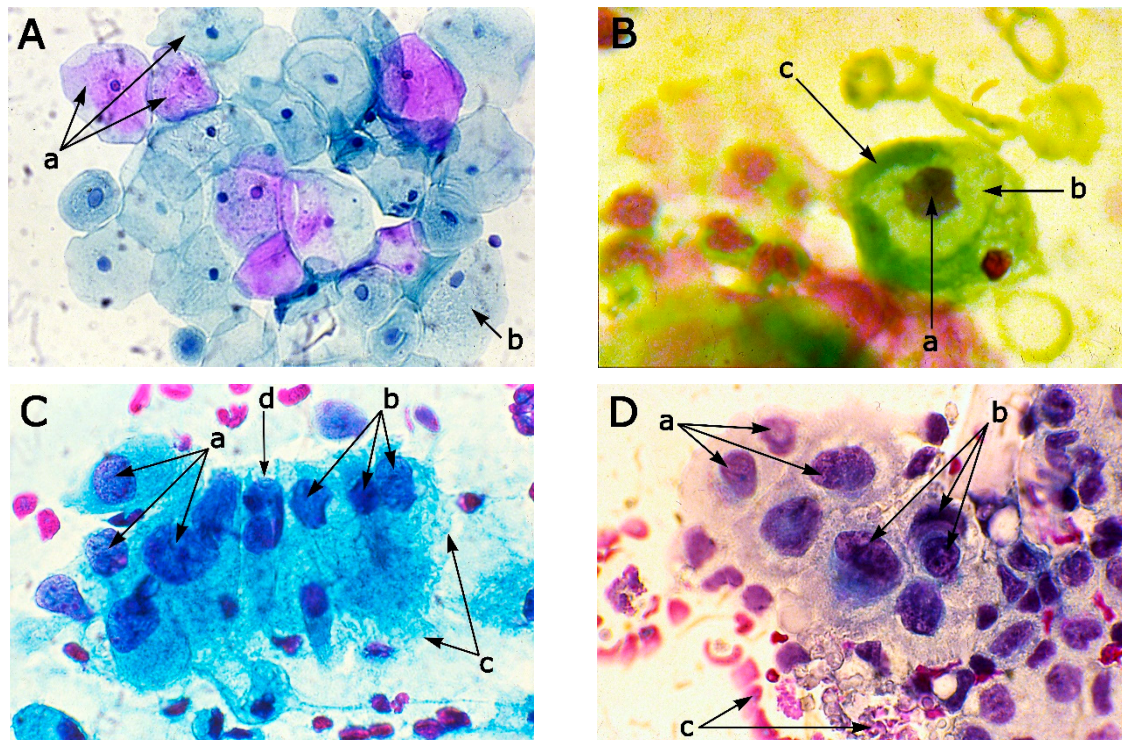


Figure 3. Cellular morphological disorder indicates pathologically mutated forces. (A) Healthy uterine cervix cells: (a) superficial squamous cells. (b) Intermedial cells. (B) LSIL—low grade squamous intraepithelial cervical cell lesion (mild precancerosis): (a) nucleoli are generally absent, nuclei are three times larger compared to those of normal intermedial cells. A variable degree of nuclear hyperchromasia. (b) Perinuclear cavitation (koilocytosis) consisting of sharply delineated clear perinuclear zone. (c) Well-defined cytoplasm. (C) HSIL—high grade squamous intraepithelial cervical cell lesion (severe precancerosis): (a) the cells are smaller than the cells in LSIL. Cell size varies. (b) The degree of nuclear enlargement is variable too. (c) Contours of nuclear membrane are quite irregular. (d) Wrinkling of nuclear membrane. (D) Invasive carcinoma cells: (a) cells are frequently smaller than healthy ones and display most of the features of HSIL cells. (b) Nuclei demonstrate coarsely clumped chromatin. (c) Tumor diathesis consists of necrotic debris of cells and old blood. Magnification: (A) 200×; (B–D) 350×; Staining: (A,C,D)—Papanicolaou [69], (B)—Pekárek [70], Kobilková and Siracký [71]. Location: (A) ectocervix of uterus; (B) vagina; (C,D) endocervical area. Nuclei—dark colors; cytoplasm—light colors.

Morphological changes of cells and tissues along the cancer transformation pathway are assessed by comparison with morphology of a cell in the healthy state. Sizes, shapes, and structures of cell membranes, nuclei, nucleoli, and chromatin are changed. Cancer cells can have more than one nuclei and the nuclear–cytoplasmic ratio is different. Differences between equal cells, nuclei, nuclear–cytoplasmic ratio, and other structures and parameters are significant. Morphological changes are connected with disturbed organization mechanism and increased effect of random events. The well-defined structure of healthy cells and their long-range arrangement in tissues require the existence of long-range forces. A disturbed electromagnetic field and related forces in cancer cells are impressed into morphological changes—the more disturbed the field, the more chaos in morphology.

4. Discussion

This paper brings a comprehensive framework of fundamental interdisciplinary mechanisms connected with cancer initiation and development, described by Pokorný et al. [9,47]. Typical biophysical processes leading to cancer are based either on parasitic energy consumption, resulting in emission of free electrons from ordered water layer at dysfunctional mitochondria, or by absorption of conducting contaminants, both damping the cellular electromagnetic field. The damped cellular electromagnetic field is followed by changes in the biochemical region. Strong controlling signals are missing and a large number of randomized chemical reactions and genome mutations is produced as coherent controlling signals are overcome by random features. The defects in biophysical and biochemical region are transferred to the biological region and result in the known biological stage of cancer. Essential biophysical processes of the cancer transformation are mutually connected with other links of pathological development of cancer.

The decisive part of the cancer transformation pathway is caused by biophysical mechanisms connected with damping by electrons in a Warburg effect cancer cell, in fibroblasts associated with a reverse Warburg effect cancer cell, and with short-circuiting by filaments contaminating a cell, dividing cancers into three basic phenotype groups. The highest probability of cancer initiation seems to be connected with parasitic energy consumption in cells. Different cancer incidence in different cell types [45], e.g., low incidence in muscle and liver cells (most liver tumors are formed by metastases) can be also explained by this mechanism. Due to abundant blood vessels, the cells have high-enough energy supply, even in the case of comparatively high parasitic energy consumption. If the parasitic consumption exceeds a critical rate, cellular death may occur instead of cancer transformation. Cell-mediated immune response to the LDH virus antigen in patients with myocardial infarction supports the idea [44]. By including fundamental biophysical processes and their disturbances into a general picture, the ideas presented in this paper represent a novel attitude to the cancer problem, shedding light on yet unexplained phenomena. Development pathways of the Warburg effect and the reverse Warburg effect cancers are presented in Figures 4 and 5. Current knowledge enables us to explain biophysical mechanisms of cancer origin and to suggest continuation and development in biochemical and biological regions. Biochemical reactions and mechanisms are presented only to demonstrate their connections and dependences.

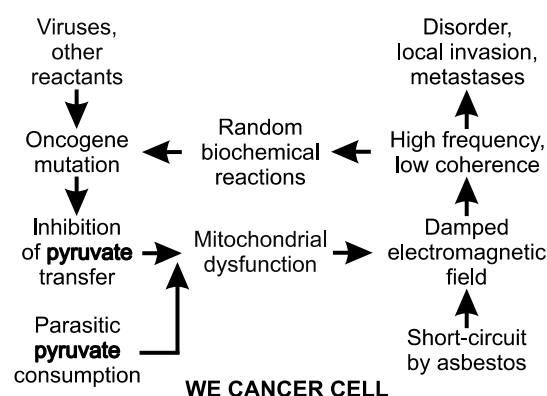


Figure 4. A schematic picture of physical pathological links in cancer development of the Warburg effect (differentiated) phenotype. Damping of the cellular electromagnetic field is the main functional link along the pathway of cancer development. The electromagnetic field can be damped by electrons released from the repolarized ordered water layers around dysfunctional mitochondria or by conducting fibers inside the cell, such as asbestos. The organization forces of electromagnetic nature in the cell are disturbed.

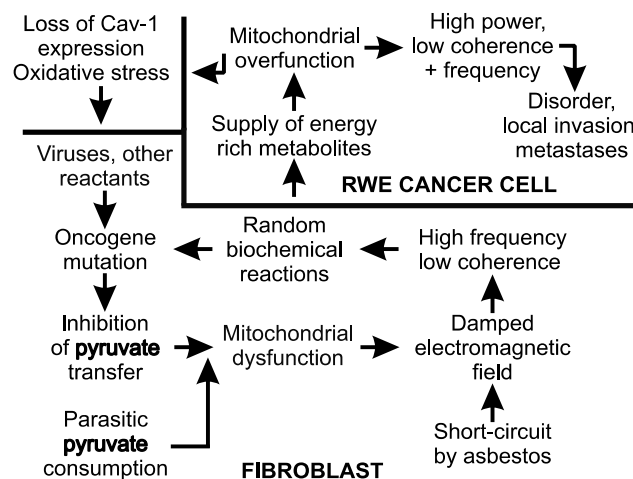


Figure 5. A schematic picture of physical pathological links in cancer development of the reverse Warburg effect (undifferentiated) phenotype. Pathological processes in a fibroblast associated with the cancer cell are similar to those in a cancer cell of the Warburg effect. Pathological transformation of the fibroblast is controlled by signaling from the tissue and from the cancer cell. Loss of stromal Cav-1 expression is a key condition for development of the reverse Warburg effect. The cancer cell is fueled by energy-rich metabolites produced by fibroblasts.

Our model is based on experimental data to a significant extent. The LAI assay data [33–37] clearly indicate that cancer development is connected with the LDH virus infection, as suggested in [63,66], or with a pathological process with a similar CMI response. Chronical infection by the LDH virus leads to decreased oxidative processes in mitochondria which corresponds to an equivalent behavior of a Warburg effect cancer cell. Decreased oxidative processes lead to a reduced transfer of H^+ ions through the inner mitochondrial membrane, resulting in an altered membrane potential [45,46]. The discrepancy in the potential values published in [45,46] can be explained by a presence and repolarization of a layer of ordered water [48] formed on the membrane. The repolarized water layer can emit electrons which increase conductivity of the cytosol. As a result, higher damping of electromagnetic field occurs, and ordering forces must be disrupted. The presence of electromagnetic field generated by living cells was experimentally confirmed [10–12], and increased damping in cancer tissue was detected [52–55]. The idea of electromagnetic control over biochemical reactions is a hypothesis only, although partially supported by a massive influence of electric field on enzymatic reactions discussed in [14,15]. If valid, the hypothesis would shed light to the origin of genome mutations in a cancer cell.

It is well-known that microparticle parameters are affected by an electric field [72,73], in particular, frequency and energy of oscillations—vibrational Stark effect [74,75]. We suggest that chemical reactions might be triggered and controlled by a coherent electromagnetic field (reverse vibrational Stark effect), which generates resonant frequency components [9]. In such a case, a virus is able to disturb the bond if it produces a resonant electromagnetic field of sufficient power (sufficient number of photons in the time of bonding) in comparison with the biological source. If the biological field is damped, the probability of virus bonding is increased. In the case of high-enough damping, randomized biochemical reactions may also occur [9], together with disturbed long-range organization forces of an electric and electromagnetic nature [76]. Numerous carcinogenic agents, such as tobacco tar, might then contribute to specificity of the mutation and thus accelerate the process of cancer initiation.

Genome mutations are known to drive cancer progression. However, their role in cancer initiation is questionable, as specific oncogene mutations are not being found in all tumors in a given cancer type, while being absent in their healthy counterparts [72]. In other words, cancer transformation can occur without a specific mutation, while the mutation itself need not necessarily lead to cancer. Our model thus explains the mechanism of cancer initiation and suggests a hypothesis on its consequence—genome mutation.

The generally presented knowledge contains only a part of cancer processes—the processes of biological and biochemical origin. Biophysical energy defects are often neglected. However, biological systems should be also viewed as physical objects—open dissipative structures with dynamic stability sustained by exchange of matter, energy and information based on specific organized structure—solitons and generation of electromagnetic field [56]. Damped cellular electromagnetic activity may cause (1) loss of resonant interaction between cells, resulting in interrupted mutual communication and ordering forces, and (2) weakening the reverse vibrational Stark effect, resulting in genome mutations. Therefore, diagnosis of cancer initiation should be based on detecting changed physical parameters, such as resonant frequencies, the presence of parasitic energy consumption, and decrease of respiration energy processes.

Preventative measures should target the suppression of parasitic energy consumption and the production of increased immunity reactions against infectious agents—mainly viruses and bacteria—which can cause damping of generated electromagnetic field and condition mitochondrial dysfunction and genome mutation.

5. Conclusions

Electromagnetic activity is a natural part of life. Cancer is a disease of the cellular energy system, a pathological disturbance of coherent cellular electromagnetic field, leading to disturbed organization forces in inflicted cells and tissues. The fundamental disturbance is formed by damping caused by electron conductivity in cytosol or by short-circuiting fibers contaminating cells. A well-known short-circuiting is caused by asbestos. Damping by free electrons occurs in Warburg effect cancer cells and in fibroblasts associated with reverse Warburg effect cancer cells. The damping electrons are released from ordered water layers around mitochondria if the pH is higher than the critical intermediate value due to decreased transport of H^+ ions across the mitochondrial membranes. Decreased transfer of H^+ ions from the mitochondrial matrix may be caused by extensive parasitic consumption of pyruvate energy, by inhibition of pyruvate transfer to mitochondria resulting from dysfunction of PDH enzymes or other defects of mitochondrial function. Damped electromagnetic field and disturbed reverse vibrational Stark effect protection might result in randomization of chemical reactions; this hypothesis may explain the occurrence of massive genome somatic mutations. Mitochondrial dysfunction is the central process triggering the development of the Warburg effect cancer cell and of the fibroblast malignant activity associated with the reverse Warburg effect cancer cells. Genome mutations then follow, rather than being the causing initiator. The main biophysical pathological links of both cancer transformation pathways are described and graphically visualized. Results of our extensive immune response study indicate precancerous conditions to be the critical phase in cancer transformation.

Cancers can be divided into three phenotypes based on their underlying mechanisms:

1. The Warburg effect (differentiated) cancer with mitochondrial dysfunction in a cancer cell is a process within a single cell. The electromagnetic field is damped, and the frequency of oscillations is increased. Gradual evolution of the pathological processes results in gradual morphological changes.
2. The reverse Warburg effect (undifferentiated) cancer is a pathological state not only of a cell but also of pathological interactions in the tissue. Fibroblasts with mitochondrial dysfunction supply energy-rich metabolites to the corresponding cancer cell. The cancer cell has fully functional mitochondria, high power of the electromagnetic field shifting oscillations to an unstable nonlinear region, and lowered frequency. Strong, unstable acting forces result in extensive morphological changes.
3. Cancer caused by short-circuiting of a cell by conducting fibers is a single-cell process with similar characteristics as Warburg effect cancers.

All three phenotypes share common properties: decreased coherence, disturbed organization forces, and changed oscillation frequencies, resulting in disrupted interaction with the tissue, local invasion, and metastases.

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