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Features of signal transmission and aqueous media in tumorogenesis

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Abstract

Background: The latest studies highlight the importance of a holistic bioelectric field in the development of tumor diseases. According to some researchers, carcinogens prevent formation of a single morphogenetic field and lead to the creation of separate bioelectric fields. It has been experimentally proved that the development of a tumor in a certain part of the body depends on the bioelectric state of the distant regions. Water is one of the important links between the morphogenetic field and molecular substrates. Due to the presence of hydrogen bonds in the aqueous media, specific structures can be formed that can receive, store and transmit information. Intracellular structured water can serve as a "transformer" of various types of energy for use in the life processes of cellular structures. It was found that normal biological tissues could be distinguished from hyperplastic and malignant ones by means of magnetic resonance image scan based on recording diverse reactions of water protons.

Conclusions: the importance of a holistic bioelectric field in the development of tumor diseases is probably paramount. The development of a tumor in a certain part of the body depends on the bioelectric state of the distant regions. It is possible that carcinogens prevent formation of a single morphogenetic field and lead to the creation of separate bioelectric fields. A more in-depth study of the bioelectric and water constituents in patients with oncopathology will probably open up new facets of oncogenesis.

Key words: carcinogenesis, bioelectric patterns, aqueous media.

Introduction

At the present stage, cancer incidence and mortality remain one of the most modern pressing challenges. According to estimates from the International Agency for Research on Cancer (IARC), cancer will be the leading cause of death in the coming decades in all regions of the world. More than 22.2 million cancer cases reported each year in the world are expected to be diagnosed by 2030 [1]. The American Cancer Society has published an annual report, which shows that 1.8 million new cancer cases and 606880 deaths from cancer are expected to occur in the USA in 2019 [2].

According to January 2019 statistics, the lowest level of five-year survival in Europe after a cancer diagnosis is seen in the Russian Federation (40%), while in France, for example, it is more than 60%, and in the USA – more than 80%. The reason is that in Russia oncological diseases are diagnosed, as a rule, at stage III or IV, while in Europe and the USA – at stage I or II [3].

Despite huge financial resources invested in cancer research, the leading U.S. centers have noted a steady decline in the incidence of certain low-risk cancers and an absolute increase in intermediate and high-risk cancers [4].

The importance of intercellular communication in oncogenesis

Despite substantial efforts aimed to identify cancer "triggers", molecular cell substrate studies have been significantly more modest. Instead of a small amount of biochemical and genetic indicators of specific blastoma cells, molecular analysis of human cancers have revealed a much wider variety of such determinants [5]. The latest studies identify a number of RNA molecules that do not encode proteins as tumor markers. According to Lavrov SA et al. [6], who investigated the aspects of non-protein-coding RNAs influence on chromatin structure, the actual scale of these processes at this stage turns out not to be evaluable, but, undoubtedly, enormous. Similar conclusions can be found in the works of many researchers [7].

Modern studies confirm the historical thesis that voltage gradients can predict morphology, providing information on the structure, growth and formation of the organism as a whole, and play an important role in the process of oncogenesis [8, 9].

The results of experiments [10] serve as an example of significance of the bioelectric state of cells in tumorigenesis.

Scientists induced tumor-like structures (ITLSs) in Xenopus model by overexpression of various oncogenes, such as Xrel3, Gli1, p53Trp248 and KrasG12D, associated with the development of melanoma, leukemia, lung cancer and rhabdomyosarcoma. Experimental findings suggest that the depolarized transmembrane potential is a marker of ITLSs regardless of its genetic origin.

According to the authors [11-13] violation of the expression of some ion channels is promising in terms of the diagnosis of blastoma processes. However, the same effect was achieved by researchers [14] using any method of Vmem depolarization (by modulating chlorine, sodium, potassium, or hydrogen channels).

The researchers [15] also point out the paramount importance of the integral formation field as contrasted with molecular mechanisms at the cellular level for the integral development of an individual. The scientists' research was focused on independent methods for implementing morphogenesis. For example, renal tubules in a triton, having a constant size, can be constructed from cells of various sizes, depending on ploidy. Reaching the same macroscopic state can be realized by various underlying molecular mechanisms. Thus, the renal tubules can be formed both by bending of the cytoskeleton – twisting one very large cell around it, or by numerous small cells.

The above discrepancies can explain to some extent the absence of a frequent direct dependence between the outcome of the cancer process and the level of tumor markers.

In the context of the importance of the problem concerning intercellular communication for tumor genesis and regenerative pattern, we think it necessary to consider the early experiments of Seilern-Aspang F and Kratochwill L [16]. The author described experiments with planaria in which a carcinogen led to the formation of many head teratomas with irregular nerves and ectopic eyes, and concluded that "the cell-isolating action of the carcinogen prevents formation of a single morphogenetic field and leads to the establishment of several separated fields of reduced dimensions".

Consequently, it is possible that in their mainstay tumors have their own bioelectric autonomous field. The latter leads to a loss of integration with the host's body layout. This phenomenon is indirectly confirmed by the fact that, in contrast to normal somatic tissues, which are reconstructed during transplantation to foreign places [17], the histopathological structure of metastases reflects the structure of the tissue of origin rather than their destination [18].

The importance of the aqueous media in oncogenesis

According to the researcher [19] bioelectric control of cell differentiation and growth can be achieved using different types of water.

Spiral-shaped chain structures can be formed during the interaction between the water molecules and the structural components of the cell, which make it possible to implement the proton conduction mechanism through this universal conductor. Water molecules can interact with each other in such formations according to the principle of charge complementarity, that is, through long-range Coulomb interaction [20].

Just in a few instances the intracellular water can be considered as solely a medium [21], nevertheless it is a metabolic reactant, product, and catalyst [22]. Intracellular water is responsible for the conformations and functions of all biomolecules due to direct interaction with their hydration shells [23-25]. According to Zenin SV [26], violation of the Arrhenius dependence in determining the thermodynamic parameters for complexation of aromatic cycles indicates the presence of a structured state of the aqueous medium that controls the behavior of interacting hydrophobic molecules.

Features of the water structure are reflected in the intracellular salt composition. A 1000-fold preference for K^+ over Na^+ has been found in a halophilic organism without any energy expenditure but with a highly reduced intracellular water mobility [27].

Measurable differences in the water structure of healthy and pathologically altered tissues and cell structures are possible to detect by magnetic resonance imaging (MRI). MRI measures the response of water protons and therefore represents differences in the aquatic environment.

Hazlewood et al. [28] found that precancerous stages could be identified by an MRI scan for hyperplastic and malignant stages. Further studies have confirmed the prospects of this method [29-31]. It would be possible to determine this diverse reaction of water protons at the level of organs, tissues and cells [32, 33] and cell structures [34, 35].

Let us consider hereinafter some structural aspects of water providing to it these properties.

Water is a substance whose main structural unit is an H_2O molecule, which consists of one oxygen atom and two hydrogen atoms.

The water molecule has a structure of a kind of isosceles triangle: an oxygen atom is located at the top of this triangle, and an atom of hydrogen at its bottom corners. The O-H bond length is 0.96 nm and the H-O-H bonds make an angle of 104.27°. These parameters relate to the hypothetical equilibrium state of the water molecule without its vibrations and rotations. Because of the large difference in electronegativity between hydrogen and oxygen atoms, electron clouds are strongly biased towards oxygen. For this reason, and also because hydrogen ion has no inner electron shells and is small, it can penetrate into the electron shell of a negatively polarized atom of a neighboring molecule. Due to this fact, each oxygen atom is attracted to the hydrogen atoms of other molecules, and vice versa. Each water molecule can participate in up to four hydrogen bonds: two hydrogen atoms – each in one, and an oxygen atom – in two; the molecules in an ice crystal are in such state. The properties of water mainly depend on the magnitude of the hydrogen bonds [36]. Authors of the article [37] note that it is impossible to give an exact definition of H-bonds and even to indicate which interactions, covalent or electrostatic, play the main role in its formation.

During the formation of hydrogen bonds, water molecules can act as electron acceptors and donors at the same time. As a result, water dimers are formed [38]. According to Tretyakov MI [39] water dimers are found in the Earth's atmosphere and influence on chemical reactions, homogeneous condensation processes and the radiation balance of the planet. Using density functional method researchers [40] performed calculations for the water dimer at 20.480 points. Attempts have also been made to determine as accurately as possible the potential for the water dimer [41]. As a result, it turned out to be so complex that it cannot be used in computer modeling. The set of parameters occupies two pages (available on http://fandango.ch.cam.ac.uk).

The real physical properties of water differ substantially from the properties of other hydrides (compounds in which hydrogen is combined with another element). In other words, unlike other substances, the properties of water cannot be calculated on the basis of its position in the periodic table of the chemical elements by Mendeleev. Theoretically, based on its position in the table, water – that is, oxygen hydride – should go into the solid phase, turn into ice at -100° C.

According to the researchers Cameron IL et al. 2013 [42], multiple unfrozen water fractions in biological materials (plant and animal tissues) were most often recorded at temperature ranges of -6.5, -15.0, -30.4, -74.0 and -96° C. Interestingly, a distinct unfrozen water fraction of 0.20 to 0.28 g/g was observed below a temperature of -74° C (vitrification state) in all samples surveyed. According to Pagnotta SE and Bruni F [43], some seeds in this state remain dormant but are germinal by rehydration above this level. At the same level of hydration, cysts of shrimp embryos remain non-metabolically viable [44].

Water and aqueous solutions have anomalous properties compared to other liquids. Water is characterized by: 1. Polymorphism of crystalline structures; 2. Maximum density at 3.98° C; 3. Decrease in molar volume when ice melts; 4. High values of melting points, boiling points; 5. When many hydrocarbons are dissolved, negative values of transfer entropy from a nonpolar solvent to water can be noted; 6. Extremely high values of surface tension; 7. Decrease of viscosity with increasing pressure; 8. High values of molar heat capacity; 9. High dielectric constant; 10. Minimum isothermal compressibility at 46.5° C [5, 47].

Due to the hydrogen bond, water molecule has a quality that manifests itself only in the presence of other molecules: the ability to form hydrogen bonds between oxygen atoms of two molecules that are close to each other. Each of the water molecules attached to this molecule is itself capable of joining further molecules. This process can be called "polymerization". Using a rapid decompression technique integrated with in situ X-ray diffraction, low-density aqueous media indicate the presence of a fully developed tetrahedral network. At the same time, there is a distinct difference in terms of the tetrahedral order parameter depending on the physical state of water [48].

The authors [49, 50] found that the resulting network structure is characterized by many small condensations, in which the molecules have four bonds and the local molecular density around them is less than the global density. According to Geiger et al. [51] liquid water can be considered as a typical polymer.

The features of the physical properties of water and the numerous short-lived hydrogen bonds between neighboring hydrogen and oxygen atoms in water molecules create favorable opportunities for the formation of special structures – associates (clusters) that perceive, store and transmit a wide variety of information [52-54].

During the process of structuring, we can conditionally distinguish several levels. At the first level, classical water molecules combine with each other, forming the minimum structural units – quanta water, each of which consisting of 57 H_2O molecules.

The second level of organization of the aqueous medium is associated with the union of quanta water into more complex water structures – associates.

The third level of structuring the aquatic environment is characterized by the combination of associates into more complex structures – supermolecules (clusters). This formation is a stable, long-living structural element of the aqueous environment.

The cluster resembles an elongated rhombus-shaped crystal. Information on the interaction between these water molecules is encoded in the structure of clusters. The pattern of hydroxyl groups on the surface of rhombohedrons ensures the memory of water. In other words, dipolar water molecules making up the crystalline facet come out of it, being charged either positively or negatively. It turns out a binary code, as in a computer. In contact with a water cluster of introduced substances or other disturbing factors, they seem to imprint their electromagnetic pattern on its facet. Subsequently, this "labeled" cluster, in contact with another, "clean" one, does the same thing – it transfers its electromagnetic pattern to it, but only in a "negative" one. The value of clusters formation in water is explained by their ability to temporarily "remember", "store", and "radiate" huge amounts of information in the form of electromagnetic waves [20, 26, 55, 56].

The above water features are supported by the theoretical conclusions of the author Bushuev IuG [57]. In his opinion, the structural heterogeneity of liquid water justifies the existence of a set of phenomenological models. The researcher believes that in the system of H-bonds in water, it is possible to define an unlimited number of structures, each of which is characterized by its structural elements and connections (relationships) between them. Currently available technical tools allow us to investigate the behavior of systems consisting of hundreds and maximum of thousands of particles.

Water as an energy substrate

The spatial structure and some physical properties of water molecules depend on the spin of hydrogen atoms. Spin (literally – rotation) is an intrinsic form of angular momentum carried by elementary particles, which has a quantum nature and is not related to the movement of the particle as a whole. Para-water is a water molecule in which the spins of both atoms are aligned in the same direction. If the electrons move in the opposite direction, we refer to ortho-water. One of the main differences between the para- and ortho-spin isomers of water is that the former has a state in which the molecule does not rotate (the rotational quantum number is zero), while ortho-spin isomer does not have such a state – it is always in motion. This difference leads to the fact that different spin isomers of water have different degrees of adsorption on the surface. It is important to note that the energy of the rotational ground state of ortho-H_2O (j=1) is 23.79 cm-1 higher than the energy of the rotational ground state of para-H_2O (j=0), i.e. energy will be released during the ortho-H_2O – para-H_2O phase transition [58, 59].

The researchers (Willitsch S et al.) [60] report the relationship between the nuclear spin, rotational symmetry and its consequences for chemical reactivity. According to the author, N_2H molecules and para-water "react 25% faster than ortho-water; this effect can be explained in terms of how the spin of hydrogen atoms nucleus influences the rotation of the entire molecule".

The existence of different spin isomers of water can explain a number of experimentally observed features of energy exchange in cell biophysics. According to the authors [61-63], the increase of metabolic activity in biological structures is associated with this phenomenon.

Energy for the vital activity of most organisms is produced by aerobic respiration. According to the definition of Antoine de Lavoisier, respiration "is nothing but a slow combustion of carbon and hydrogen, which is entirely similar to that which occurs in a lighted candle, and that, from this point of view, animals that respire are true combustible bodies that burn and consume themselves. The final products of the combustion of carbon and hydrogen are carbon dioxide and water" [64].

Aerobic respiration is currently reduced to mitochondrial respiration. Here oxygen acts as a final electron acceptor that donates its energy to the electron transport chain for the synthesis of ATP molecules. As energy portions released during this process are equivalent to quanta of middle-far IR-photons (≤0.5 eV), mitochondrial respiration is analogous not to burning, but to smoldering combustion.

Genuine combustion is a stepwise reduction of oxygen to water with four electrons ("one electron reduction"). By these means, quanta of energy equivalent to energy of visible and even UV-photons (> 1 eV) are generated [65].

Almost half a century ago, Albert St. Gyordi suggested that cellular metabolism could be supported by the energy released during the direct reduction of oxygen to water. The scientist noted that cyanide, which blocks the activation of oxygen, causes rapid death, although the ATP supply in the tissues remains quite large for a long time. The described phenomenon indicates the need for continuous activation of oxygen to maintain vital activity. The author asks: "Does this not mean that there are two independent energy generation systems, both using O_2 as an electron acceptor?" [66American immunologists pointed out the possibility of water burning in living matter in 2000. Researchers noted that antibodies (immunoglobulins) and some other proteins (including beta-galactosidase, beta-lactalbumin, and ovalbumin) catalyze oxidation of water with singlet (excited) oxygen to form hydrogen peroxide, which is equivalent to water burning [67]. It was found that water is the electron donor, specially arranged by these proteins [68]. This means that water can form such structures in which it acquires the properties of a reductant. Pollack defined water adjacent to hydrophilic surfaces as the "Exclusion Zone Water (EZ-water)" [69].

According to Pollack et al., the electrogenic properties of EZ-water and its potential with respect to the bulk water are largely determined by the properties of the surface that forms EZ-water. The larger the surface area and the density of its fixed negative charge, the greater the electron-donor capacitance of EZ-water of this surface is [70]. Nucleic acids have the maximum charge density among biopolymers, and DNA has an uttermost surface area. Therefore, DNA must have a maximum density of structural energy and the ability to organize and manage the environment. EZ-water has special properties – EZ-water has negative electrical potential (it reaches 150 mV) with respect to the bulk water adjacent to it. A direct current flows through a conductor connecting an electrode placed in EZ-water and an electrode in volumetric water, the strength of which increases at illumination. At illumination of EZ-water by infrared radiation with λ = 270 nm, it emits fluorescence [71]. If charged microspheres ranging in diameter from 0.5 to 2 μm are suspended in the water bordering to hydrophilic surfaces, they are quickly displaced from the boundary water regardless of the nature of the gel and the charge sign of the microspheres. The width of the microsphere-free water layer reaches hundreds of microns [72].

Accordingly, in an aqueous system in which EZ-water and bulk water are adjacent, a small activation energy is sufficient for the transfer of electrons to oxygen and the entire chain of one-electron oxygen reduction to be realized.

The structural temperature of EZ-water is lower than bulk water [73] and EZ-water constantly extracts thermal energy from the environment thus maintaining its electron-donor capacity. Such a water system is not a generator, but a transformer of heat energy into electronic excitation energy.

The process can be initiated by an external pulse, but only if both the oxygen concentration and the electron reserve (electron-donating capacity of EZ-water) exceed certain threshold values [74]. When the electron-donating capacity of EZ-water falls below threshold levels, the combustion wave is dampened until a sufficient layer of EZ water is restored by recruiting water from the volume into it. The reaction becomes rhythmic and can provide a cyclic course of coupled reactions [75].

In the light of the above data on the energy-informational role of water, let us try to analyze some features of tumorigenesis.

Studying the growth dynamics of Ehrlich ascites tumor, the author Zamay T. [76], found that the growth curve of tumor cells did not correlate with their energy supply. The research results showed that, starting from the 7th and up to the 12th day, the energy state of ascites cells markedly worsened. On the 12th day, the state of the studied structures was characterized by the poorest energy supply (the ratio of inorganic phosphate and nucleotide triphosphates was maximum at this time). However, during this period, the maximum acceleration of tumor growth was observed. It was also surprising that blastoma cells showed very high viability in the terminal phase of the development of the cell population, despite the fact that the number of cells in the state of apoptosis was 25% from the 11th to the 14th day. Moreover, by the 16th day, when the mass death of tumor-bearing mice was already observed, it increased even to 78%.

The researcher explains the described phenomenon by the genomic instability of the tumor and the accelerated mutational process that contributes to the emergence of cells that are characterized by the highest viability in worsening conditions. Taking into consideration the given literature, the phenomenon observed by the authors may have another explanation. To clarify our assumptions, let us consider the mechanism of apoptosis in detail.

Apoptosis is a process of programmed cell death by forming apoptotic bodies without violating the integrity of biomembranes. The phenomenon is not accompanied by the development of the inflammatory process and happens without macroscopic signs, structural or functional defects of the tissue [77, 78]. The importance of this phenomenon for the formation of both organs and the body as a whole is enormous. Apoptosis provides the proper ratio of the number of different cell types, the removal of genetically damaged cells, and the selection in cell populations. In an adult, programmed cell death balances mitotic division, provides tissue renewal by maintaining optimal cell numbers [79]. As an example, we can cite an increase in the number of endothelial cells and the dimensions of blood vessels in mice with targeted inactivation of the Braf gene that controls apoptosis of endothelial cells [80]. There is a massive neuronal cell death, reaching 25-75% of the entire neuronal population, starting from the early stage of development of the nervous system, and throughout life activity. According to Paparone S et al. [81], the delicate balance between apoptosis and cell survival regulates the development of the nervous system and homeostasis.

It was noted that apoptotic cells near the amputation site provided an increased source of Wnt3, which regulates division of neighboring stem cells. Thus, pattern information was spread by dying cells to proliferating ones [82, 83].

According to more relevant data, in blastoma cells of the tumor tissue, it is noted overexpression of mitochondrial oligomers K-Ras, BAD, p27, Bax and Bak that increase glycolysis to provide energy demand during the formation of apoptotic bodies – blebbishield [84]. The latter probably indicates the active (inducing) participation of the tumor in the process, most likely as a highly organized structure, providing itself for the next stage in the development with a substrate in the form of apoptotic cells and not a conglomerate of solitary tumor cells.

The short last stage of development indicates a low likelihood of the emergence of a *de novo* tumor cell strain. According to the author Zamay T [76] the failure of the tumor proliferation curve was observed on the 12th day and then, during the course of the day, cell population switched back to active growth. In this case, we support our assumptions by referring to the author's opinion Moiseenko VM, Galante E et al. [85, 86]. The scientists have noted that the duration of breast cancer growth from both 1 cell and 103 cells (in the case of polyclonal origin) until the clinical manifestation cannot even theoretically last several months (as previously thought), because in this case, tumor doubling time should be less than 1 day. Meanwhile, the maximum growth rate of primary breast cancer in humans is 3-8 days.

Coming back to the main topic of our research – the peculiarities of the aqueous structure of the tumor, we recall that the properties of EZ-water and its potential are largely determined by the properties of the surface that forms EZ-water.

Considering the observation of the author Zamay T [76], we can assume that the maximum acceleration of tumor growth on the 12th day under the conditions of the worst energy supply is associated with a peculiar quantitative-qualitative transition. It is possibly the critical summation of pattern information from apoptotic cells and its transmission to proliferating cells through aqueous structures during this period. In a similar vein, it is important to note the observations of Kozhokaru A et al. [87]. The authors argue that excited water molecules that have received additional energy are able to transfer it to the same structures and molecules of other living organisms (detectors), which have similar frequencies of electromagnetic waves.

Perhaps the phenomenon observed by the author Zamay T [76], was also accompanied by a transition to another type of energy metabolism not directly related to ordinary molecular substrates. This possibility is evidenced by the fact that it is impossible to detect about 30% of cancers by FDG-PET research, suggesting that these tumors use alternative (non-glucose) metabolic pathways to produce energy [88].

As previously noted, EZ-water is able to extract thermal energy from the environment by transforming low-density energy (heat) into high-density energy, into electronic excitation energy. For example, at illumination of EZ-water by infrared radiation with λ=3100 the fourfold increase in its thickness is observed. Infrared light is literally free energy and is found everywhere – it is not only inside, but also outside [71].

Another possible source of energy for tumor proliferation not directly related to conventional molecular substrates may be weak and superweak magnetic fields – relic radiation (RR), geomagnetic field. According to Kozhokaru AF et al. [87], the energy of the polarized component of the relic radiation (RR), which is a superweak cosmic photon radiation, can be absorbed by excited atomic electrons by NMR. As previously stated, EZ-water may be used as the acceptor. In experiments on mice with transplanted tumors Novikov VV [89], showed that the action of weak combined, constant (30-49 μT) and variable (frequencies 3.5-5.0 Hz, amplitude 50-120 nT) magnetic fields modulate the development of ascites and solid forms of Mouse Ehrlich ascites carcinoma (EAC).

If the above statements are true, the maximum acceleration of tumor growth as a conglomerate of tumor cells arising *de novo* for 1 day under the conditions of the worst energy supply is unlikely. This phenomenon is probably inherent in a highly organized biological structure with the ability to structure water very specifically. The latter quality probably allows the tumor to choose energy sources depending on the phases of development or other factors.

Conclusions

Summarizing the above materials, it can be concluded that the importance of a holistic bioelectric field in the development of tumor diseases is probably paramount. As it was shown, the development of a tumor in a certain part of the body depends on the bioelectric state of the distant regions. It is possible that carcinogens prevent formation of a single morphogenetic field and lead to the creation of separate bioelectric fields. The cited materials indicate the binding role of the aqueous medium in relation to the field and molecular components of biological objects. Despite the impressive amount of research on water structures, this substance, in spite of its apparent simplicity, remains little studied.

However, the evidence that exists at the present stage indicates that water, perhaps, acts as a kind of mirror of objective reality, capable of not only reflecting the world in all its endless images, but also conveying the inner essence of processes.

An *in vivo* study of the various properties of water in blastoma cells and tissues, and extrapolation of the obtained data, will probably allow opening up new aspects of the etiopathogenesis of oncological diseases.

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