

Is it possible to stop cancer mechanisms; by controlling cell's redox

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Abstract: This review article have provided molecular insights into how functional characteristics that could be involved in cancer mechanisms. There was an attempt of treating cancer patient dogs (Leukemia and Prostate) with the help of Electro-chemical activated water (ECA-solutions). The attempts were revealed 100 % curing success. It could be, though, that the mutations contribute to the carcinogenic process by impairing the function of the respiratory chain. Reactive oxygen species (ROS) play role in progenitor activation, signaling and escaping apoptosis cells, and genetic damage. There is evidence that the cell's loss of electron-donor properties is followed by its transfer into ontogenesis. ECA and ERW (Electrically Reduced Water) -solutions on cellular level adjust electron-donor and receptor properties of the cell, directly affect organoids and intracellular molecular complexes, leading to repairing the expression and cell signals. Action of ECA and ERW -solutions prevent ontogenesis, suppresses tumor angiogenesis by scavenging intracellular ROS and suppressing the gene expression and secretion of vascular endothelial growth factor.

Keywords: Carcinogenic process; Cell signals; Electro-chemical activated water; Reactive oxygen species.

Introduction

Tumors are the result of localized, unregulated, cell growth. For a tumor to become malignant, cells must begin to metastasize (move), and invade other tissues. The original tumor is called a primary tumor, and all the cells derive from single aberrant cell. As tumors metastasize the new colonies, or foci, are referred to as secondary tumors or metastatic centers. Each center will arise from a different founder cell but all will derive from the single founder cell of the primary tumor.

Cell signaling is part of a complex system [1], of communication that governs basic cellular activities and coordinates cell actions. The ability of cells to perceive and correctly respond to their microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis. Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, and diabetes. By understanding cell signaling, diseases may be treated effectively and, theoretically, artificial tissues may be created.

In normal cells, growth, division, and differentiation are highly regulated processes. Some signaling molecules (growth factors) promote cell division. Other signaling molecules cause cells to stop growing. Many signaling

molecules, including growth factors and growth inhibitors, bind to receptors on the surface of the cell. In many cases, these receptors must interact with one another, or dimerize, before they can become fully activated. Once they are activated, receptors activate relay teams of proteins inside the cell (signaling pathways) [2].

Activated signaling pathways carry messages from the receptor to the inside of the cell and sometimes all the way to the DNA in the nucleus. Activation of these signaling pathways is often carried out by the transfer of chemicals, called phosphates, from one member of the relay team to the next. This process is known as phosphorylation. Receptors and other proteins that perform phosphorylation are called kinases [3,2]. The messages carried by the activated signaling pathways lead to the accumulation and activation of certain proteins that either promote or inhibit cell growth and division. The rate of cell growth and division depends on the balance of these two types of signals.

Cancer is thought to be mutations in genes for signal transduction components, the first indications of this came from studies of DNA tumor viruses that infected non-human vertebrates. It was established that particular genes in the genomes of these viruses (termed oncogenes) were responsible for tumor promotion. With time and the convergence of cellular and viral oncology, it was realized that oncogenes were the mutant counterparts of normal

cellular genes. The cellular genes are called proto-oncogenes. Many of the cellular counterparts of oncogenes have now been identified (and cloned), and it is clear that most are components of some form of signal transduction pathway. The signaling systems are used by cells to make decisions like grow/don't grow, move/don't move or change patterns of gene expression. Many of these cellular components are the same kinds of factors to be the driving forces behind the fundamental mechanisms of developmental decision making. Little wonder then that the mechanisms that control development and go out of control in cancer seem so intimately related. Characteristically, oncogenes derange growth regulation by hyperactivating growth stimulatory signals; thus normal growth control is overridden. Because the mutations generally produce an over stimulation of a positive signal, only one mutant copy of the gene is required to provide the phenotype. Consistent with this, most oncogenes are dominant mutations.

There is, however, another way to get over stimulation of a positive signal. That is to have a recessive, loss of function, mutation in a negative regulator of the signal. This is the basis for another group of genes found to be mutant in many cancers; called tumor suppressor genes or anti-oncogenes (neither name is completely satisfying). One of the clearest indications of the existence of such genes came from experiments in which tumor-producing and non-tumor-producing cells were fused together. With rare exceptions (which turned out to be important) the fused cells were non-tumorigenic (suppressing tumor formation).

Cancer production

One of the fundamental traits of cancer cells is their ability to proliferate without a controlled signaling input. They achieve this in a number of ways: Increasing growth factor

production, Stimulating normal cells in the microenvironment to provide cancer cells with growth factors, increasing the number of receptors on the cell surface, structurally altering receptors to facilitate cancer cell signaling and activating proteins in the downstream signaling pathway. Recent studies also highlight the ability of cancer cells to disrupt negative feedback loops that constitute a safety mechanism to dampen a signaling pathway whenever a mitogenic signal is hyperactivated. One key example of this is the RAS oncoprotein. Oncogenic activity of RAS is not the result of overactive RAS signaling but rather the disruption of normal negative feedback mechanisms operated by the oncogenic GTPase. Other examples of this process include loss-of-function mutations in phosphatase and tensin homolog (PTEN), which amplify phosphatidylinositol 3-kinase (PI3K) signaling.

Tissue invasion and metastasis are integral components in how tumor cells escape from the primary site and disseminate into distant organs. The process of tissue invasion and metastasis is not well understood, but, in general, it involves changes in the way cells attach to other cells and to the extracellular matrix [4, 5].

Immune surveillance is an essential cellular process that proactively prevents tumor formation in the human body. Preclinical studies have suggested that an active immune system continuously recognizes and eliminates the vast majority of cancer cells before they establish themselves and form a tumor mass [4,5].

In tumor cells, the process of angiogenesis, or the formation of new blood vessels, is critical for sustained tumor growth and metastasis. Tumor angiogenesis is a multistep process and involves signaling input from several pro-angiogenic growth factors [4, 5, 6].

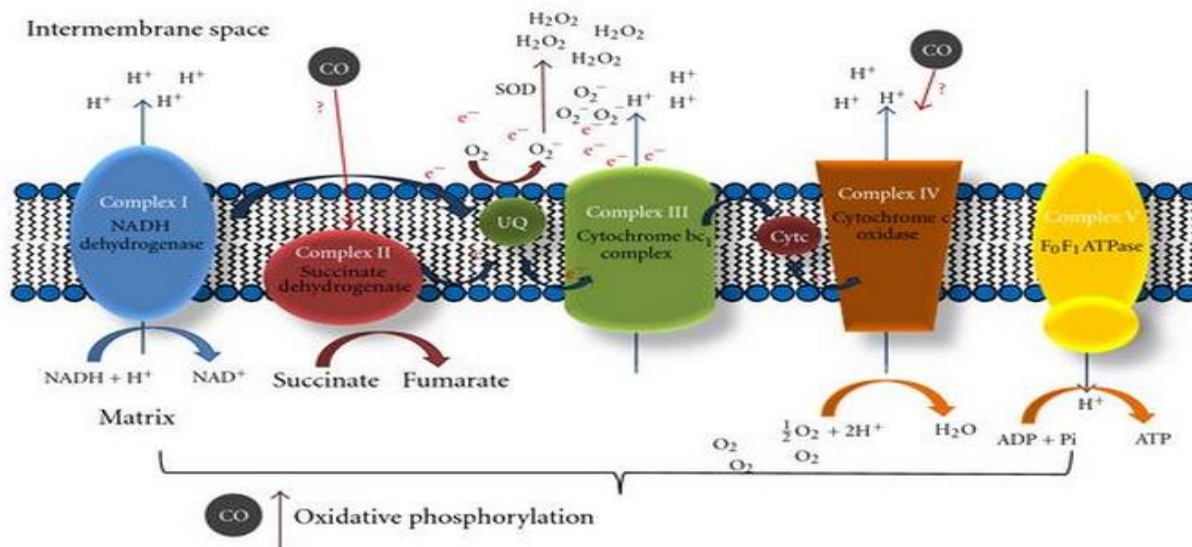


Figure 1: Every living cell needs energy. The source of energy that is used by a cell varies depending on for example the cell type and its environment. The key players of metabolism, catalyzing the chemical reactions, are enzymes. Mitochondria contain the enzyme complexes of metabolic processes, most of the adenosine triphosphate (ATP), which is the molecule essential for many energy-requiring reactions in the cell, is generated in mitochondria. Mitochondria also contain their own genetic material; mitochondrial DNA (mtDNA).

Cancer is a redox disease?

Every living cell needs energy. The source of energy that is used by a cell varies depending on for example the cell type and its environment. In every cell the energy needs to be converted in order to be accessible for energy-requiring

processes such as growth, organization, transport and reproduction. Metabolism is a set of chemical reactions involved in the uptake, conversion, digestion and excretion of energy-containing nutrients.

There is growing realization that cancer is not primarily a genetic disease, but an epigenetic response to chronic stress. Cancer cells, however, depend heavily on glycolysis to obtain energy, even though plenty of oxygen is present. This phenomenon – aerobic glycolysis subsequently known as the Warburg effect - prompted Warburg to propose that mitochondrial dysfunction was the primary cause of cancer. Aerobic glycolysis is a robust hallmark of most tumours; it involves a high uptake of glucose with lactate production in the presence of oxygen, lactate being the by-product of pyruvate, even in those cancer cells that appear to have working mitochondria. The reason seems to be that cancer cells need glycolysis to generate carbon skeletons for the synthesis of proteins and nucleic acids to support rapid cell proliferation; and blocking glycolysis does appear to inhibit cancer cells (though it would also affect normal cells). Reduction and oxidation always go together, hence ‘redox’ reactions. Redox reactions are the heart of energy transduction in living organisms. Electrons move according to the *reduction potential* (also referred to as reduction-oxidation potential or redox potential), the affinity of a substance for electrons. The redox potential for each substance is compared to that of hydrogen, which is set arbitrarily to zero at standard conditions of 25 °C, 1 atmosphere, and 1 M concentration [7].

ROS play multiple roles in the hallmarks of cancers and in ligand-independent RTK transactivation, decreased RTK activation threshold [8]. It is involved in p53 activation, loss of contact inhibition, and loss of anchorage dependence [9]. ROS play a role in Met overexpression, matrix metalloproteinase secretion, in vadopodia formation, and plasticity in cell motility, EMT [10].

ROS are involved in expression of telomerase and in increasing the rates of mutation, increasing sensibility to mutagenic agents, and compromising the surveillance systems [11].

Energy metabolism of cancer cells

Cancer cells, to a much higher extent than normal cells, rely on glycolysis for production of ATP [12]. This phenomenon is called “aerobic glycolysis”, or the Warburg effect, and has been known for over 50 years to be a common feature of tumor cells. The mechanisms of reprogramming are complex, involving activation or deactivation of a large number of genes [13].

The amino-acid substitutions found in colon cancer resulted in a lowered Cytochrom oxidase (Cyt_cO) activity as compared to the wild-type enzyme. A lowered Cyt_cO catalytic activity could lead to a decreased rate of electron flux through the entire respiratory chain and thus insufficient amounts of ATP being produced. In addition, with the Tyr33His Cyt_cO the oxygen reduction was uncoupled from proton pumping. A decreased synthesis of ATP through oxidative phosphorylation might however not be as devastating for a cancer cell as for a normal cell, due to the metabolic shift occurring in tumors. In fact, a defective

respiratory-chain activity could contribute to initiating the metabolic reprogramming that occurs in cancer cells.

Amino-acid substitutions in Cyt_cO have been found for example in prostate cancer, pancreatic cancer and ovarian cancer. In addition, substitutions in Cyt_cO have been reported in normal colonic crypt stem cells in colon cancer patients [14, 15].

Several studies have shown that chemical inhibition of Cyt_cO activity could in fact lead to increased ROS formation from other respiratory-chain complexes. An increased ROS production due to Cyt_cO inhibition by azide has been observed in both mammalian cells and submitochondrial particles [16, 17, 18]. In these cases the suggested mechanism is that the inhibition of Cyt_cO causes an increased leak of electrons, and hence ROS formation.

Discussion

Mechanisms of Cell genotoxic stress control

The ability of cells to maintain genomic integrity is vital for cell survival and proliferation. Lack of fidelity in DNA replication and maintenance can result in deleterious mutations leading to cancer. Surveillance control mechanisms that check to ensure proper completion of early events and cellular integrity before initiation of subsequent events in cell cycle progression are referred to as cell cycle checkpoints and can generate a transient delay that provides the cell more time to repair damage before progressing to the next phase of the cycle. A variety of cellular responses are elicited that function in checkpoint signaling to inhibit cyclin/Cdk activities. These responses include the p53-dependent and p53-independent induction of Cdk inhibitors and the p53-independent inhibitory phosphorylation of Cdk molecules themselves. Several human heritable cancer-prone syndromes known to alter DNA stability have been found to have defects in checkpoint surveillance pathways. Exposures to several common sources of genotoxic stress, including oxidative stress, ionizing radiation, UV radiation, and the genotoxic compound benzo(a)pyrene, elicit cell cycle checkpoint responses that show both similarities and differences in their molecular signaling [19,20].

However, there is evidence that the cell’s loss of electron-donor properties is followed by its transfer into such a phase of individual development (ontogenesis) whose histological characteristics are similar to those of the phenomenon of functional-morphological differentiation associated with the loss of normal proliferation activity and subsequent aging or malignization.

Suggested novel therapy

Electrochemically activated water (ECA-water) Hypothetical mechanisms of ECA-solutions’ action on a cellular level

Water as a pure chemical substance or as a solvent of aqua-mineral media of mineralization no higher than ≈5 g/l subjected to unipolar electrochemical treatment, metastable, possessing anomalous reactional and catalytic activity and relaxation electron-unbalanced (electron-donor or electron-acceptor) qualities.

Action of ECA-solutions on cellular objects seems to be carried out in several conventional ways. Stable and metastable products of electrochemical synthesis directly

affect lipid membranes, cell organoids and intracellular molecular complexes and chemical compounds. Oxidizing and reducing agents of ECA-solutions alter the ORP of peri- and intracellular media, thus regulating the activity of endogenous biooxidants and bioantioxidants. Shifts of ORP gradient on biological membranes affect transfer of substances in the cell due to electroosmosis. Penetration of structurally altered water inside the cell activates aqueous media of cytoplasm and speeds up biochemical reactions taking place there.

Anolyte kills cancer cells

Strong oxidants, among them electron-acceptor anolyte factors, cause cell membranes' damage, which, in its turn, negatively affects electron-donor properties of the cell. Electron-acceptor action of anodically activated solutions on bio-membranes is universal, since anolyte contains a variety of over-oxidized chemical forms, dissolved in a medium with a pathologically high ORP value. Because of that, acids and peroxides being a part of anolyte react with a cell object on the background of enhancing electron-donor qualities of biological fluids, which are a basis of biological substrate of peri- and intracellular system.

Anolyte is a complex of stable and metastable strong oxidants in an aqueous medium of super-high electron-acceptor activity, capable of quick propagation through biological barriers and passing of its electron-acceptor abilities via amorphous substrates. That creates prerequisites for a totally penetrative oxidation effect similar to that of general irradiation radiolysis. Therefore, anolyte (oxidant) and radiation load on the body or particular tissue systems are to have a number of common pathophysiological (for cancer cells) or therapeutic effects (for normal cells).

Catholyte augments cell regeneration and development

“Alkaline (cathodic, “live”) water certainly augments cell regeneration and development.

Oxidative phosphorylation reaction goes on according to the following formula: $RN + NaClO \rightarrow ROH + NaCl$, where R stands for organic radical, RH is organic hydrophobic compound, ROH – oxidative hydroxylation product. ROH derivatives are low toxic, hydrophilic and can be easily removed thanks to physiological excretion.

It can be added that balance of anti-radical chain elements seems to be a necessary but insufficient prerequisite for efficient suppression of free radicals' activity, since electron transfer in accordance with the system: enzymatic oxidation products \rightarrow NADP-H \rightarrow glutathione \rightarrow ascorbate \rightarrow tocopherol, depends on the ORP value of fluid media, among which there is an anti-radical defense system. Catholyte is the only means of non-reagent shift of biological fluids ORP towards electron-donor values. Increased tissue reductive potential ($\Delta ORP < 0$) stimulates the transfer of two hydrogen atoms from the substrate to NADP. At that, NADP is reduced: a proton and an electron add to a nicotine-amide radical, and another electron adds to its N-atom, which due to that loses its charge. A proton corresponding to this electron remains in the medium and raises its $[H^+]$ content.

According to the findings of studying laboratory and agricultural animals, receiving catholyte for drinking, the following conclusions can be made. Catholyte of drinking

water or aqua-saline solutions with pH of about 9.0–9.5; ORP about (-400 ± 50) mV, CSE at its ingestion at a volume equivalent to $10 \pm 5\%$ of daily intake of drinking water produces the following effects on the organism of mammals and birds: General invigorating action - Increases resistance of the body to ionizing irradiation and Elevates activity of tissue respiration enzymes [21].

There was an attempt of treating cancer patient dogs (Leukemia and Prostate) with the help of ECA-solutions. It started by i/v injection of one ml of anolyte per 10 kg live body weight daily for 2 weeks. At the same time treatment implied indication of shock doses of anolyte (450 ml per day) during 3 days followed by drinking catholyte doses of 300 ml daily during 5 days. Similar course with slight dosage alterations was repeated after 3 and 20 day intervals. The attempts were revealed 100 % curing success [22].

Electrically Reduced Water (ERW) (Anti-cancer effects)

ERW causes telomere shortening in cancer cells [23]. It suppresses tumor angiogenesis by scavenging intracellular ROS and suppressing the gene expression and secretion of vascular endothelial growth factor [24]. ERW suppresses the growth of cancer cells and microorganisms [25,26] and induces apoptosis together with glutathione in human leukemia HL60 cells [27]. ERW induces differentiation of K562 cells to megakaryocytes [28], and when supplemented with Pt nanoparticles, it strongly suppresses the two step transformation of NIH3T3 cells by a carcinogen [29].

Conclusion

Oxidative stress has been linked to cancer. The signaling systems are used by cells to make decisions like grow/don't grow, move/don't move or change patterns of gene expression.

There is evidence that the cell's loss of electron-donor properties is followed by its transfer into such a phase of individual development (ontogenesis)

So, we think that action of ECA and ERW -solutions on cellular level adjust electron-donor and receptor properties of the cell, prevent ontogenesis, suppresses tumor angiogenesis by scavenging intracellular ROS and suppressing the gene expression and secretion of vascular endothelial growth factor.

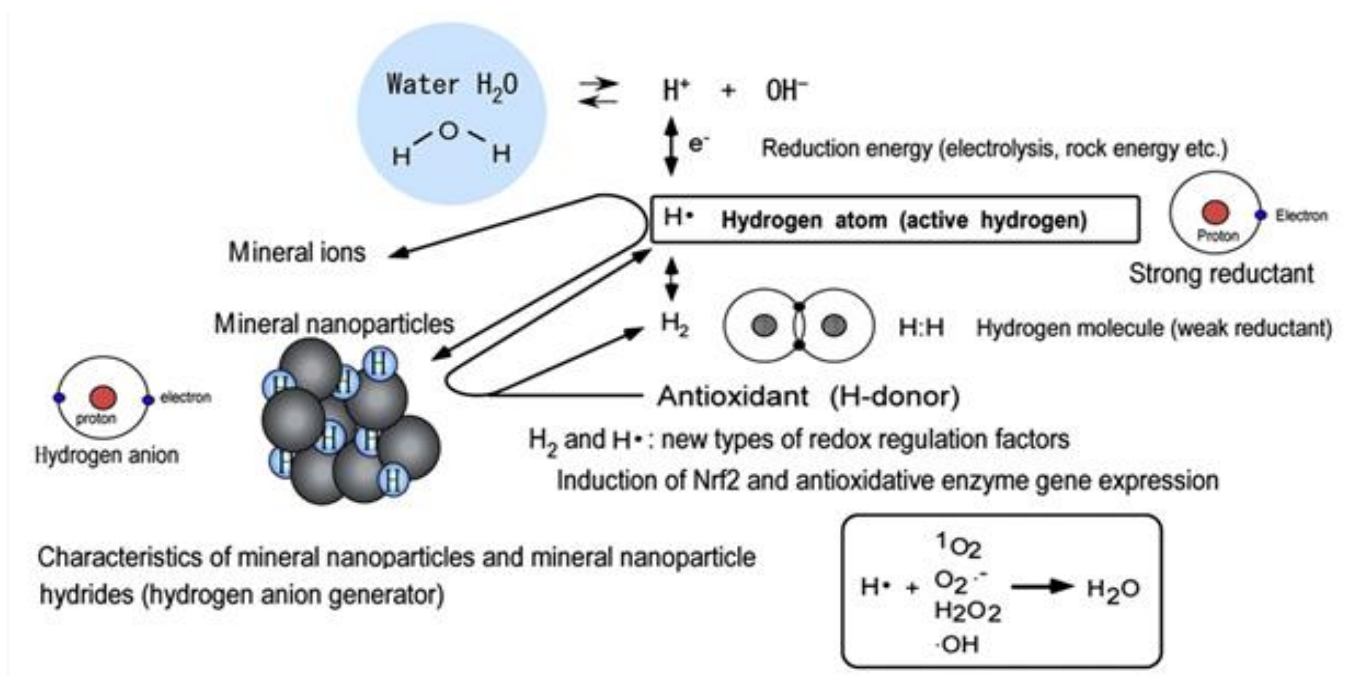


Figure 2: ERW, water is reduced by electric energy, rock energy and other energy to produce active hydrogen (H atom) and mineral nanoparticles. H atoms produce hydrogen molecules, which are weak reductants, but can function as H-donors. Mineral nanoparticles sustain reduction energy, because they gradually dissociate to mineral ions, releasing electrons. Mineral nanoparticles directly scavenge O_2 , $\cdot OH$ and H_2O_2 by catalysis mechanisms [30].

Conflict of interest

The author has declared no conflict of interest

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