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Review Article

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Cancer: An Unexpectedly Critical Role of Cell Water?

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Abstract

A fresh approach to cancer etiology is introduced. The approach rests on the recent recognition that EZ/fourth-phase water ordinarily fills the cell. A consequence is that the negative charge of EZ water arguably creates the cell's negative electrical potential. If so, then the fact that cancer cells have consistently low electrical potential implies a shortage of EZ water. In healthy cells, when low potential maintained for some time, mitosis is triggered. Hence, cancer cells' sustained low electrical potential may be pivotal: it may underlie the rampant cell division that is one of cancer's hallmarks. Effective therapeutic routes may involve methods to build EZ water and thereby increase the cell's electrical potential. Some such routes suggested. If the thesis is on target, then those routes may have promise in dealing effectively with reversing, or even preventing, cancer.

Keywords: Cancer; Water; Electrical potential; Cell division; Therapeutics

Background

In exploring the underlying mechanism of cancer, rarely does the influence of cell water enter into consideration. Nor is water thought to play much of a role in the biology of the cell, except perhaps as a background carrier of the more important molecules of life. Indeed, biological water has long seemed practically irrelevant. Yet, it was the oft-labeled 'father' of modern biochemistry, Albert Szent-Gyorgyi, who famously opined, "Life is water dancing to the tune of solids." Szent-Gyorgyi made it abundantly clear that water was not merely a passive entity but a central player in all of life's processes.

On the shoulders of towering scientific giants such as Szent-Gyorgyi stand the identification of water's fourth phase [1]. That phase comprises an ordered array of molecules. The ordered array builds next to hydrophilic (water-loving) surfaces, both biological and non-biological. That would include proteins, lipids, and nucleic acids. If such solids densely populate the cell, then logically, the cell should be packed with fourth-phase water, sometimes referred to as "***exclusion-zone" or "EZ" water***.

Evidence that EZ water does indeed fill the cell emerges most directly from the work of Gilbert Ling. In numerous published papers and several books [2,3], Ling presented voluminous experimental evidence that the cell was filled with "structured" water. The generic term "structured" refers to molecules arranged in some kind of ordered array. Often reflexively dismissed, Ling spent the better part of his life establishing that such ordered water fills the cell. It was the nature of that ordering that we were able to discern experimentally, eventually characterizing its unique features and labeling it "fourth-phase" water. A simple way of demonstrating the presence of fourth-phase, rather than liquid, water in your cells is to cut yourself. If cells were filled with liquid water as generally presumed, that water should flow from the cut as it might flow from a breached water pipe. But it does not. Blood emerges, but water remains. It's evidently not liquid water that fills the cell, but a kind of viscous water that clings to the solids inside the cell.

As EZ water's presence is a relatively recent observation, the question whether it might play a pivotal role in the genesis of cancer has only just begun to be considered. A 2019 book, titled Cancer and the New Biology of Water [4] puts structured (EZ) water at the center of cancer development. A 2023 paper, titled Structured Water and Cancer [5] deals with the role of EZ water in cancer largely in the context of biochemical/metabolic issues.

Like those authors, I will argue that EZ/fourth phase water might be a critical issue in cancer, and I will present the underlying logic, relevant evidence, and clinical implications. In short, I will argue

that a shortage of intracellular EZ water could be key to the rampant cell division that is often a dominant feature of cancer. Before proceeding, I must mention that the very existence of fourth-phase water has aroused controversy. Several investigators deeply immersed in water science have proposed an alternative interpretation of the evidence that we have uncovered [6-11]. Their arguments have centered largely on certain unusual physicochemical features of Nafion, a polymeric material used in many of our studies to nucleate the growth of EZ water. Those features are purported to lead to an alternative explanation, centered on the phenomenon of "diffusionphoresis," i.e., the diffusion of ions from within the Nafion polymer.

An issue with this interpretation is that similar results are obtained using many nucleating materials whose character differs qualitatively from that of Nafion. Those materials include the following: hydrogels [12], fats [13], ion-exchange resins [14], membranes [15], clay [16], various biological surfaces [17], metals [18] — even magnets [19] and single monolayers [20], where internal ion diffusion would seem implausible. Thus, generalized arguments centered on diffusionary features unique to Nafion would seem irrelevant in those instances. Water's fourth-phase appears to be a general feature of the aqueous environment, on which many applications are rapidly building.

Hence, I proceed. If the cell is indeed filled with EZ water, what might that imply in terms of cancer etiology? Cancer characteristics are mostly known: cells become increasingly dysfunctional and often divide incessantly. How might EZ water play a role? Getting there involves an understanding of how EZ water relates to the cell's electrical potential, and how the magnitude of that potential may trigger cell division. That is the direction we are headed.

EZ Water and Origin of the Cell's Negative Electrical Potential

A notable feature of EZ water is its electrical charge. Microelectrodes plunged into the EZ have generally shown negative electrical potential [21]. This feature raises a critical question: if EZ water bears negative charge and the cell is filled with EZ water, then how much of the cell's negative electrical potential might arise from cell water? It is widely thought that the cell's electrical potential derives from the action of its membranous components: ion channels and pumps. Those entities' combined action is said to bring ions into and out of the cell. If more negative than positive ions are brought into the cell, then the cell ought to contain net negative charge.

While evidence exists to support that contention, I believe that the overall view may be invalid. I have previously argued that much or perhaps all of the cell's negative electrical potential arises not from the action of membranous components, but from the presence of cell water [22]. Here, I briefly cite a few of those arguments. If the cell's negativity arises from components of its membrane, then breaching the membrane should create a short circuit, obliterating that negativity and killing the cell. But it does not. Even the extreme act of slicing the cell in two results in survival [23], without any evidence of membrane resealing [24,25]. Membrane pumps and channels would be obliged to maintain the electrical potential despite the anticipated massive ion leak — something akin to blasting a hole in the floor of a huge water-tank and maintaining the tank's water level by adding a succession of water droplets. Not reasonable.

A similar conclusion derives from simple logic. The cell has been long thought of as a cytoplasmic gel enveloped by a continuous membrane [26]. The cell bears negative electrical potential. But gels alone exhibit similar negative electrical potentials [27-29] even though they contain no membrane. Logically, then, the cell's negativity would appear to arise in the cytoplasmic gel, not the membrane, i.e., from the negative charge of the EZ water that comprises the gel.

Additional supporting arguments appear not only in a publication [22], but also in the bodies of two books [1,30]. I believe those arguments point to a cytoplasmic origin of the cell's negative electrical potential, even though mainstream science believes otherwise. If the cell's negative electrical potential arises in the cytoplasm and the cytoplasm is filled with negatively charged EZ water, then the cell's negative electrical potential would appear to originate from EZ water. The logic seems straightforward. I'm aware that any such assertion may be taken as unlikely, for it challenges many years of accumulated understanding. But if it is potentially relevant for approaching the etiology of cancer, then perhaps it's worthwhile withholding judgement for the time being and seeing where this seemingly radical position might take us.

From this point on, we assume that the cell's electrical potential arises from the presence of EZ water. Where does this presumption lead?

Implications of the Cell's Negative Electrical Potential

Though we have implicitly implied that the cell's negative electrical potential (i.e., the potential difference between inside and outside of the cell) remains constant, that is not always so; it can have dynamic features. In excitable cells, the so-called "action potential," the sharp transition from negative potential to near zero, is thought to trigger cellular action. In the mammalian ventricle for example, the resting cellular potential sits at negative ~90 mV. It sharply transitions to near zero as the heart begins to contract, remaining there during the period of contraction, finally returning to -90 mV as the cell relaxes. Comparable phasic electrical changes are characteristic of the action in many excitable cell types.

Cellular action, on the other hand, involves transitions in both proteins and water. Half the pages of my first book on water [30] detail evidence in multiple cell types that cellular action involves not just proteins transitioning from extended to folded states, but also water transitioning from structured to the ordinary liquid-water state. Actions involve both proteins and water. Taken together, such transitions are generally classified as "phase transitions," phenomena well recognized in the discipline of physical chemistry.

The two phenomena described above, action potential and phase transition, are widely thought to exist as separate events: The action potential serves as the trigger, while the phase transition constitutes the triggered action. No reason has existed to think of the two phenomena as aspects of a single mechanism.

Until now

At the time of publication of my 2001 book (30), we had not yet carried out the experiments showing that "structured" water bore negative charge. We had thought of that water in the same terms as did Gilbert Ling: an ordered array of water molecules. We were thus unaware that a transition from structured to unstructured water might involve a change of electrical potential from negative to zero. We now know that it does: biologically structured (EZ) water bears negative charge while liquid water bears no charge. Thus, the phase transition itself could bear responsibility for the action potential. The two phenomena could be manifestations of a single mechanism.

I mention this dynamic not only because of its simplifying nature, but also to emphasize the critical character of the cell's electrical potential. It is not an adjunct feature but a direct reflection of what's happening inside the cell.

Electrical Potential and Cancer Cells

How might these features of electrical potential relate to the issue of cancer?

While the magnitude of the stable electrical potential may vary among different cells, typically it lies in the range of -50 mV to -100 mV. When we were carrying out electrophysiological measurements during early career, we knew that when the electrical potential was of smaller magnitude, the cell might be struggling to stay alive and it was time to switch to specimens with more normal electrical potentials. Others knew the same. That experience squares with the idea of the electrical potential as a critical feature of cell function. For the cell to operate properly, it must maintain a robust negative electrical potential.

Thus, a striking clue comes from the electrical potential of cancer cells. That potential magnitude is consistently small. Compared to the electrical potential of most normal cells, cancer cells exhibit potentials on the order of only 10 - 15 mV. That low electrical potential is seen over diverse cancer-cell types [31-35]. It is a characteristic feature.

If the cell's negative electrical potential derives from the presence of EZ water, i.e., if its magnitude is a reflection of the amount of EZ water in the cell, then the small magnitudes of electrical potential in cancer cells indicates something significant: those cells may lack very much EZ water. This observation is key to the arguments that will follow.

The implied low EZ content seems consistent with morphological considerations. Cancer cells are often (though not always) observed to be "dedifferentiated." Structures characteristic of healthy cells are in short supply. Organelles are sparse. The cell seems structurally rather empty, much like embryonic stem cells. Hence, the material surfaces needed to nucleate EZ growth are largely absent, and it is therefore no surprise that EZ water is in short supply. Much of the water seen in cancer cells may well be ordinary liquid water.

There is, indeed, a confirmed change in water structure when normal cells turn cancerous [36]. Magnetic Resonance Imaging (MRI) and atomic force microscopy (AFM) both reveal that cancer-cell water differs from that of healthy cell water [37-39]. If normal cell water is rich in EZ, cancer cells may not be. The implication seems clear. If cell function —arguably, the phase transition — depends on a robust amount of EZ water and cancer cells lack very much of that water, then the cancer cell cannot function as its normal counterpart. It is dysfunctional. It is dysfunctional because the EZ required for the ordinary phase transition is not available.

On the other hand, it is not merely dysfunction that characterizes the cancer cell, but also the proclivity to divide. Might the rampant cell division relate to the cancer cell's consistently low electrical potential? Could that low potential be a clue?

Electrical Potential and Cell Division

Why do tumors frequently grow uncontrollably?

Cells ordinarily divide by a well-studied process known as mitosis. The mitotic spindle, a characteristic structure, parses duplicate chromosomes into daughter cells, which then separate. One cell becomes two.

Key to that process is the electrical potential. Half a century ago, pioneering studies were carried out in the laboratory of Clarence Cone [40,41]. Cone showed that the cellular electrical potential varied throughout the mitotic cycle. That evidence convinced him that such variations might exercise control over the cell cycle. By altering the cellular ionic content to achieve high magnitude electrical potential, Cone was able to block mitosis; and oppositely, by provoking sustained depolarization, mitosis could be induced [41]. On the basis of those observations, Cone argued for a direct role of

the cell's electrical potential in cell division [42].

Cone's observation on the induction of mitosis through sustained depolarization leads rather directly to an hypothesis about cancer's origin. Key is the cancer cells' low electrical potential. That low potential could direct those cells to proceed through mitosis as though they had been triggered to do so. Low electrical potential facilitates the process, just as it does in ordinary mitosis. The cell should continue to divide as long as its electrical potential remains low.

Similar considerations could well apply in embryonic cells, where frequent division is characteristic. Largely undifferentiated and actively dividing, embryonic cells have low magnitude electrical potential, while more mature cells with substantial intracellular structure and not dividing have high magnitude electrical potential [43-46]. Hence, the electrical potential paradigm advanced for cancer cells may also apply to embryonic cells.

The pervasive generality: low electrical potential leads to sustained cell division. I'm not the first to relate the low electrical potential to cancer [47].

What's new is that we may now better understand the reasons why the low electrical potential can facilitate sustained cellular division.

EZ Water's Role in Cancer

The "why" questions of cancer can be addressed from an understanding of the origin of the cell's electrical potential — which I argue (above) comes from the presence of EZ water. The low electrical potential of the cancer cell implies that the cell contains not very much EZ water. Hence, the question of cancer could boil down to the following: [1] why can't cancer cells build much EZ water? And [2], why should the absence of EZ water promote mitosis?

The first question's answer may lie in the observation that not all hydrophilic surfaces build EZ water. Many do; some do not. We found recently that the ability of hydrophilic surfaces to build substantial amounts of EZ water depends on the distribution of charges on those surfaces [48]. If charge positions match the (fixed) positions of opposite charges on the honeycomb EZ sheet, then the EZ builds in substantial amounts. Otherwise, buildup is more restricted or absent.

A speculation, then, is that the charge distributions on natural biological surfaces match well the distributions on EZ. Hence, EZ's grow abundantly. That very feature, the ability to nucleate EZ-water buildup, may well stand as a hallmark of natural structures including proteins, nucleic acids, lipids, etc. That character may be lost in situations in which the expressed substance has been altered by a mutation of DNA structure. Whether by dint of toxin exposure, radiation damage, or the action of any of a number of other carcinogens, the altered structures may no longer have the capacity to nucleate effective growth of EZ water. Hence, the cell would contain less EZ water and the electrical potential magnitude would diminish. At the same time, the substances created by the mutated DNA might be nonviable, and therefore expelled from the cell. That could be a reason why cancer cells often appear to be as empty as they do. Emptiness, in turn, means that the surfaces required to nucleate EZ growth are in short supply; hence, EZ water itself would be in short supply.

Now to the second question: Why should the presence of liquid water, which seems to replace EZ water, promote cell division? Here, I refer to my 2001 book, Cells, Gels, and the Engines of Life [30], where I present evidence that the transition from structured (now EZ) water to liquid water ordinarily initiates cellular action. For facilitating mitotic action, then, the liquid state appears to be necessary, as molecules suspended in liquid water can move rather freely, whereas in EZ water they cannot. That requirement is met in the cancer cell, which contains abundant liquid water. Hence, mitosis can proceed unchecked. Cells continue to divide, and tumors therefore continue to grow.

Ultimately, that is the central feature proposed to underlie cancer: unchecked cell division. That process transpires arguably because the cell remains in a state that facilitates mitosis. Cells continue to divide relentlessly. And, along with that relentless division, the empty cell may be unable to function.

The Role of Local Environment

One of cancer's more enigmatic features is the critical role of the local environment. When a cancer cell is placed in a tissue consisting of healthy cells, the cancer cell becomes normal; and conversely, when a normal cell is placed in cancerous tissue, it becomes cancerous [49,50]. The evident role of environment has seemed puzzling in the context of a field dominated by genetic considerations, where the dominant feature should be the nucleus, not the local environment.

But that is not necessarily so in the present context. Healthy cells contain abundant negativity. When a low-negativity cancer cell is inserted in the healthy tissue's negatively charged environment, electrons should flow from the healthy cells to the electron-starved cancer cell, restoring its high electrical potential and thereby repressing cell division. Hence, the cancer cell should return to normal. Similarly, when a healthy cell is placed in cancerous tissue, electrons from the healthy cell should flow naturally to the surrounding low-voltage tissue. That outflow should quickly deplete the healthy cell of electrons, reducing its electrical potential and triggering incessant cell division. Hence, the healthy cell becomes cancerous.

Thus, the seemingly puzzling role of local environment may have

ready interpretation in the context of the new paradigm. The critical factor may be charge flow.

Possible Therapeutic Pathways

More than a half century ago, US President Nixon declared "war on cancer." Many would argue that war has not been won. Practically everyone among us has either suffered from cancer or knows people who have suffered. Despite multiple advances, cancer remains deeply endemic.

If the thesis presented here is on track, then new opportunities arise for dealing with both cancer prevention and cancer treatment. In terms of prevention, the obvious approach involves avoiding the known cancer-promoting agents: environmental poisons, radiation, certain electric fields, smoking, etc. What's new is the hypothesized pathway of action of all such agents: compromised EZ buildup, causing a reduction of the cell's electrical potential and triggering the relentless cell division that practically defines cancer.

Follow-up research could focus on the extent to which potential cancer-causing agents impair EZ buildup. Glyphosate, for example, the primary substance in weed killer and strongly implicated in both non-Hodgkin's lymphoma [51] and various other cancers [52], diminishes EZ water at all concentrations [53]. That finding fits the hypothesis. Whether as a class, substances that are carcinogenic impair EZ buildup remains to be explored. If strong correlation is found in future research, then a simple method of testing for carcinogenicity could be at hand: measuring the impact of the substance on EZ buildup.

Equally defined is the implied treatment. Agents that build EZ water, thereby increasing the cell-potential magnitude, should prevent rampant cell division. Those agents are predicted to qualify as anti-cancer expedients. Some cancer cells, on the other hand, may be sufficiently aberrant as to resist very much EZ buildup. In those cases, the EZ-buildup approach would only serve as a partial solution. But a potential rescue comes into play: Building EZ water in the less profoundly aberrant cells makes the local environment more negative. Regions of local negativity could then supply electrons to the more profoundly cancerous cells, thereby building EZ water in those cells as well.

Various studies have begun to identify agents that build EZ water. I present ten such agents, which are listed solely to permit further research and promote scientific understanding. All such vehicles are hypothesized to qualify as anti-cancer agents.

- Hydration. Imbibed water gets fractionally converted into EZ water. That conversion may account for the remarkable role of drinking water in health restoration, a classical example of which is the study of incarcerated Iranian political dissidents, whose impaired health could be restored simply by drinking large amounts of water [54]. By allowing the conversion of liquid water to EZ water, the imbibed water should thereby defend against cell division and cancer.
- Juicing. Wellness practitioners broadly advocate the practice of crushing the leaves of freshly grown plants and drinking the extracted liquids. Those liquids contain the plants' intracellular water, which, in healthy specimens should be principally EZ water. By drinking that juice (rather than the uncrushed leaves that contain the juice, which would quickly fill you up), EZ water is directly infused into the body, helping to support a robust negative electrical potential and thereby fight cancer.
- Drinking EZ water. Ample amounts of EZ water are contained in certain spring waters. Also, a growing number of companies produce waters claimed, but not consistently proved, to contain substantial amounts of EZ, or fourth-phase, water. Drinking such water (in volumes sufficient to avert neutralization by the modest quantity stomach acid) can provide direct infusion of EZ water into the body. From the imbibed EZ, electrons can then build the cancer cells' EZ and thereby restore health.
- Sunshine. Half the energy of the sun lies in the infrared spectral range, the range that builds EZ water [55]. Prolonged exposure to sunlight should therefore act to increase the cellular potential and thereby exert an anti-cancer effect.
- Sauna. Saunas generate abundant heat, which essentially corresponds to infrared energy. IR energy, in turn, builds EZ water. The anticipated increase of EZ-based electrical potential should inhibit rampant cell division and thereby act to help stem cancer's progress. Saunas should help.
- Herbs. We studied various herbs and other agents recognized throughout the ages to promote health. Those agents include turmeric, holy basil, coconut water, even ghee [56]. All of them build EZ water [53]. Hence, all should exhibit anti-cancer action.
- Electrical charge input. Imposing electric fields of certain frequencies but not others appears to build EZ water [57]. Those frequencies should increase cell potential and thereby inhibit cell division. By so doing, they should serve as anti-cancer agents.
- Earthing/Grounding. Flow of electrons into water converts the liquid water into EZ water [58,59]. Thus, connecting yourself electrically to the negatively charged earth and allowing electrons to flow into your body should similarly build EZ water and thereby act to thwart cancer.
- Electrons. Injecting electrons directly into the body of a tumor should, similarly, build EZ water and thereby act to eradicate the cancer. This procedure was successfully demonstrated in patients by the Swedish radiologist, Bjorn Nordenstrom [60].

His work has remained controversial notwithstanding his distinction as President of the Nobel Assembly. Followup research would seem urgently needed.

- Hyperbaric Oxygen Therapy. We found experimentally that the two principal agents of hyperbaric oxygen therapy, elevated oxygen and elevated pressure, both expand the EZ [61]. Hence, a potential basis for this anti-cancer therapy now seems evident: increasing EZ and negative electrical potential, thereby inhibiting rampant cell division. Some clinics regularly use hyperbaric oxygen therapy to treat cancer.

In sum, an array of therapeutic approaches exists to build EZ water. Some of them are routinely used for cancer treatment; others are relatively new and untested. If cancer indeed arises from EZ-deficient, low-voltage triggering of cell division, then these therapies may offer a directed therapeutic approach to healing. They remain to be explored in detail in further research.

Conclusion

I have attempted to offer a fresh perspective on the etiology of cancer, along with possible therapeutic approaches that logically follow. The new perspective involves several features that may be unfamiliar to many readers; hence, skepticism is anticipated. Those features are nevertheless underpinned by appreciable experimental evidence and transparent logic, and I invite the interested reader to explore that evidence in detail in the cited sources.

Along the way, I have indicated various areas where further research could be useful. Such studies could provide supporting or contradictory evidence. Studies of more direct nature could be directed specifically at the hypothesized mechanism, e.g., direct measurements of EZ-water content in cells undergoing rampant cell division vs. their normal counterparts.

To many readers, the approach outlined here may seem too simple. Those immersed in cancer research have struggled, some for more than half a century, to find answers. Failure to solve the cancer problem has led to the pervasive sense among researchers that the issue must be extremely complicated. Hence, the simple paradigm offered here may seem unrealistic. Perhaps it is. On the other hand, it's only recently that fourth-phase water and its inherent electrical charge have become evident. If the fourth-phase phenomenon is indeed key, as suggested, then the simplicity of the proffered paradigm can be rationalized, and readily tested.

I invite the reader to examine the evidence quoted here. That includes not only the published papers cited, but also the two books on water [1,30], which largely summarize published evidence and meld it into a cohesive interpretational framework. That framework constitutes much of this article's foundational basis, and it rests on extensive experimental evidence. I'm hopeful that the principles here articulated will lend fresh, meaningful direction to dealing with one of humanity's long term scourges. For sure, the time has come to bring cancer's eradication.

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