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Cancer and pH—A Prospective

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Abstract

How can cancer develop in so many different organs in so many different ways, but the outcome is similar enough to all be under the same title—cancer? There are so many causes of cancer—viruses, genetic defects, sunburn, gastroesophageal reflux, smoking, alcohol, radiation, chemicals, etc. The above variable well known etiologies of cancer could all induce a need for repair which involves alkalinizing the cells involved. Thus the commonality for cancers could be a pH change. If true, this could give the field of cancer prevention and therapy new avenues of pursuit.

Keywords

Cancer, Warburg Effect, pH, Cellular Pumps, Channels, Transporters, Isoenzymes

1. Introduction

Perhaps cancer, despite how you come to develop it, is in short a repair system gone awry. One can look at the long list of known potential causes of cancer and recognize there would need to be a repair process following exposure for many of them if not all of them. The more often you asked the repair system to intermittently function, especially as it aged, the more likely errors could occur.

2. History

The Warburg effect has been known for over 50 years. Basically in cancer cells, glucose is transformed into lactic acid even under aerobic conditions—through more utilization of the glycolytic pathway than would have been expected [1]. The cells could be making an increased amount of metabolic acidosis products that at least partially would be being excreted. Oxidative phosphorylation changes to aerobic glycolysis. Glycolysis is generally optimum under alkaline pH [2] which would be maintained if the acidic products were transported to the extracellular space. Warburg found a similar condition in embryonic cells (so pH may be more variable and better tolerated in stem cells, etc. perhaps even making products reinforcing growth which unfortunately is not new healthy growth but instead cancerous growth). Finally Lynen, around the same time as Warburg, found oxida-

tive phosphorylation in the mitochondria was also inexplicably decreased in cancer cells [1]. But we have known since 1968 as pH increases there is a decrease in mitochondria function [3].

3. Cellular Repair

To repair tissue through replication, cells intracellularly become more alkaline [4]. This makes sense since the histones are more alkaline and positively charged while DNA is more acidic and negatively charged. Possibly the more often repair is done, the more likely a replication error will occur. Think of a copy of a copy of a copy—monoclonal. The more often the cells possibly become intracellularly alkaline the more likely there could be activation of an error already present but not activated previously. In brief, possibly the multiple inducers of cancer may generate an error or indirectly activate an error already there, through intracellular alkalization in an attempt to help cell repair.

Possibly as a cell becomes more and more intracellular alkaline, the faster the cell may be able to replicate and the less likely the cell is to do its normal functions, making its typical products. The extracellular space will become more acidic as protons are extruded from the intracellular space. This will also tend to make the cell less responsive—resistant to normal stimuli. For example, pH changes could impact typical enzyme function, hormone binding to receptors, the conversion of prohormones to their more active hormone forms, hormone binding to theircarrier proteins, tyrosine kinase, microRNA, post transcriptional changes, etc. This could explain how sometimes hormones appear present but not as functional as usual in cancer cells. DNA methylation and modification of the histone proteins, key factors in gene expression regulation, could also be impacted by pH changes. Cell membranes and their receptors, cellular pumps, channels, and transporters could all be altered by either intracellular and/or extracellular pH changes and vice versa.

Interestingly VEGF (vascular endothelial growth factor) is more active in acidic areas [5] so the tumor, if solid and significantly changing the extravascular space pH will actually be inducing its own blood supply. While the extracellular outer ring of expanding tumor would also be inducing apoptosis, like a conquering army to normal tissue, since apoptosis is more active in acidosis [6].

4. Tumor Markers

Some tumor markers that seem relatively unrelated to the normal tissue the cancer originated from could be in fact products from the significant alkalization of the intracellular space since another group of isoenzyme and cellular machinery could be more active. Sometimes the same tumor marker can be found in several very different cancers. Tumor markers are often elevated in situations of inflammation even when cancer is not present, but probably cell repair would be ongoing [7]. Thus if cell repair is at the initial center of the development of the later possible step of cancer, the presence of tumor markers in cases of repair (without cancer yet being present) is suggestive.

5. Cancer and the Developmental Stages of Fruit

At first, the tumor mass would be alkaline intracellularly but as massive rapid growth occurs the center of the mass will possibly become more acidic as the blood supply is shifted to the rapidly expanding outer ring. Thus the center of a solid tumor could become acidic and actually go through apoptosis although at one time those same cells may have been very different. If one does an analysis of a piece of fruit it will have several stages—probably solid cancers do as well.

Having stages and expanding rings could impact our research causing conflicting results. The outer most extracellular ring would be possibly acidic as normal tissue is destroyed and cellular pumps, channels, and transporters pump acid outwards. While just inside the expanding outer extracellular ring, could be an intracellular expanding ring that was alkaline. Finally, as clinicians often find with solid tumors, the center of the mass could be going significantly acidic with loss of blood flow and eventually apoptosis actually liquefying sometimes. Thus, one needs to measure pH in the expanding intracellular outer ring which could be alkaline and not average the whole mass.

6. Isoenzymes and Cancer

One has to wonder why isoenzymes exist. Why do life forms from single cells to complex mammals have mul-

tiple isoenzymes instead of just one enzyme for a particular function? In short, why do many of life forms' major enzymes have 5 - 10 or more isoenzymes and why does this appear to be conserved by evolution?

One explanation for why there could be a need for multiple isoenzymes possibly is a as-yet-unknown episodic regional pH variability. Perhaps organelles and organs in larger life forms have pH levels that vary up and down with normal physiological situations. In humans we have known for many years there is variability in the pH levels of the stomach—acidic, and duodenal area—alkaline—a more than 10,000 fold difference in hydrogen ions. Perhaps there is pH variability also for example in the liver—the chemical enzyme manufacturing plant of the human body.

If the pH levels during certain physiological situations rose or lowered episodically, one isoenzyme might become more functional than another isoenzyme since often they have variable optimum pH levels. Indeed, years ago the optimum pH level was one of the ways individuals differentiated different isoenzymes [8].

If different isoenzymes are becoming more functional under certain conditions such as a variation in pH, then the organism could be using the particular isoenzyme to help return the organism to homeostasis. Thus in some cases the products of the isoenzyme could be an attempt to help the organism correct itself. There could be a back and forth movement similar to the tacking movement of a sailboat.

In regard to the manufacture and concentration of the isoenzymes, the enzyme can be from one or multiple gene loci and some enzymes undergo post transcriptional changes to make the isoenzyme types. Thus the environment the enzyme finds itself may be the very thing that helps influence which isoenzyme predominates especially in regard to post transcriptional changes. The isoenzyme that would be the most functional would be the one helping the organism attempt to return to homeostasis. Thus there could be a crude feedback loop which tells the system that the amount of isoenzyme is adequate. Think of foot wear—they all cover our feet but we wear boots for certain activities, sneakers for others, and dress shoes for another. We have to have them all accessible but if we can, we have the type we use the most readily available. Thus the presence of a specific isoenzyme in a specific amount is probably not a random act.

Therefore if there is one predominate type of isoenzyme for alkaline phosphatase in bone and another different one predominate type in liver, it is theoretically possible this could at least partially explain cancer metastasis. The Internal Medicine Resident is routinely asked on patient rounds by their supervisory Attending what area of the body does such and such a cancer usually metastasis to—in short we have known for decades a particular cancer is likely to metastasis to a certain organ system. The metastatic cells shower multiple areas but usually grow best in a few areas.

The specific isoenzymes' concentration may be variable. We have long known, for example, in congenital adrenal hyperplasia that a partial enzyme deficiency can cause significant long term changes. The dramatic absence shows up shortly after birth, while the partial can cause late onset changes [9]. If an isoenzyme was supposed to be "X" amount but instead was "X minus 10%", we might not notice a difference right away, but instead the individual might over time, notice a slowly progressive difference due to that reduction by 10%. Indeed a slowly progressive difference is what we see in the course of many cancers and other diseases. This could also be part of the explanation for why cancer cells don't maintain all their usual functions. It is possible their usual set of isoenzymes are not as functional as they had previously been.

7. The Mix

The mix of cellular pumps, transporters, channels, and isoenzymes a specific individual may have been born with, make that individual more susceptible to a particular cancer. Obviously anyone such as a family member with a similar combination would also have a predisposition. Some cancer inducers could cause at least some of their effect directly upon the pumps, transporters, channels, and isoenzymes or the genes making them—also impacting the general overall repair system.

There are multiple types of cellular pumps, channels, and transporters—so the poor functioning of one may be able to be partially replaced by the redundant backup systems. However the system may not be functioning optimally—think of a spare tire on a vehicle.

There may be pH swings that are dramatic but many may be for example 0.1 - 0.3. Since the optimum pH is often a bell curve, if the 0.2 change occurs in the sharply rising arm part of the bell curve then the small change of 0.2 could cause for example a change in function of say 15%. A change in function of an enzyme or hormone could be significant even though the instigating factor of a pH change of 0.2 does not seem that significant. The placement of the optimum functional pH curves may not be a random act.

These pH changes will be difficult to measure since obviously the carbon dioxide and oxygen will potentially be able to diffuse off, as for example with an arterial blood gas (unless and arterial blood gas is run right away and/or put on ice the arterial blood gas results can be skewed for oxygen, pH, and carbon dioxide). Sometimes detailed well designed experiments done *in vitro* cannot be duplicated *in vivo*—perhaps this is one of the reasons on occasion.

8. Conclusion

Cancer is in short very possibly a repair system gone awry involving pH changes. In the future, addressing cellular pumps, channels, transporters, and isoenzymes could help impact this set of diseases as well as eventually be the beginning of individualized medicine.

Disclosures

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