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The Impact of Mutations: The Future of Cancer

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Abstract:

Can cancer be predicted early? Why are people born color blind? How are mutations passed on? From color blindness, muscular dystrophy, and cancer to even the polymorphism that occurs to cause blue eyes, mutations are a crucial topic to understand in the scientific community. Mutations are alterations in genetic sequences, such as when the body codes for the wrong gene, whether it be due to an environmental factor or an intrinsic factor. In this article, we will explain how cancerous mutations work, and address potential ways to improve cancer diagnosis and treatment in the future.

DNA Sequence

TAC CCG CCA AAG TAA GGA ACA TGA	Normal
TAC CCG CC G AAG TAA GGA ACA TGA	Silent Mutation (Same Protein)
TAC CCG CC_ AAG TAA GGA ACA TGA	Deletion (Causes Frameshift)
TAC CCG CCA AA AG TAA GGA ACA TGA	Insertion (Causes Frameshift)
TAC CCG CCA AAG TAA GGA AC_ TGA	Nonsense Mutation (Stop Codon)

How do Mutations Occur?

Mutations occur in two primary ways. Hereditary mutations occur randomly due to errors in the repair process during DNA replication and protein synthesis. However, acquired mutations occur either when epigenetic factors cause issues with gene regulation or when random de novo mutations spontaneously change DNA [1].

Hereditary mutations, those that happen during the formation and repair process, can affect humans from the time that they are born. Some examples of hereditary mutations are those that cause genetic disorders such as cystic fibrosis, Tay-Sachs, sickle cell anemia, Downs Syndrome, and Turner syndrome. In these cases, gametes usually have a mutation, and once the gametes meet to form a zygote, they pass the mutation onto the DNA of the zygote. Since hereditary mutations are present from the moment of conception, genetic disorders they cause are difficult to cure.

Acquired mutations can occur due to a variety of factors, such as smoking, ultraviolet radiation, and sunlight. Chemical mutagens can enter the body through exposure by touch, inhalation, or some other factor [2]. Often, these mutagens cause cells to either alter DNA expression by deamination or a frameshift mutation. This problem proceeds to become a much more widespread genetic problem as the DNA replicates. Other types of radiation can also cause mutations. In these cases, cross-linking and rearrangement are more common, which can cause DNA breaks [3].

Finally, de novo mutations are spontaneous changes in DNA that are often present in *all* body cells. Often, the mutation occurs immediately after the egg and sperm have formed a zygote and start to reproduce, thereby replicating the mutation as mitosis occurs. These types of mutations can often be fixed by the DNA reparation process, but when they are not caught, they can wreak havoc on the body's natural processes [3].

Effects of Mutations

Harmless mutations that occur with a frequency of over 1% in the population are called polymorphisms [7, 9]. Common polymorphisms include mutations that cause variations in physical traits such as hair color, blood type, and eye color. These traits don't disadvantage individuals, but some can be a departure from standard genetic traits, such as blue eyes, which originated from a genetic mutation thousands of years ago [3]. There is, however, a portion of mutations that cause genetic problems. The malignant mutations we will discuss will be cancer-related.

Some overarching commonalities exist when looking at cancer as a subject:

- Cancer is very rarely present at birth, suggesting that cancerous mutations accumulate through environmental factors such as radiation and toxins a majority of the time.
- Tumor Suppressor genes such as BRCA 1 and p53 are important for regulating cell cycles by repairing DNA. When these genes mutate, cells grow and replicate rapidly, which can cause tumors. Over 50% of cancers are caused by mutations of the p53 gene.

- Oncogenes also are part of the cancer formation process. These genes are responsible for turning healthy cells into cancer cells.
- Cancerous mutations, fundamentally, are caused by a mutation in the cell repair and replication cycle, which causes cells to replicate rapidly. [4]

This information demonstrates what has to occur for a tumor to metastasize. First, a mutation must occur in a tumor suppressor gene such as p53. Next, this mutation promotes oncogenes to stimulate cell division, which in turn replicates a mutation into a larger population of cells. This cycle repeats, and eventually, there is a large collection of rapidly dividing cells that needs nutrients. Tumors that metastasize redirect blood vessels and nutrients in a system towards themselves. In doing so, they weaken the body in that location while simultaneously providing nutrients to cancer cells.

Why Is This Important?

This information is important in the fight against cancer. As most people know, cancer is one of the biggest problems facing the world today, as it accounts for over 20% of deaths yearly, and about 38.4% of men and women will be diagnosed with cancer sometime in their lives [5]. The understanding of cancer dynamics is constantly evolving through increased research into the metabolism of tumor growth. Unfortunately, science's knowledge of cancer has improved without significant advancements in technology to fight it. Effective therapies have stayed the same over the recent course of time [8].

The Future of Cancer Diagnosis: How Can We Improve?

The effectiveness of cancer treatments currently available depends heavily upon the stage in which the cancer is detected. Whereas localized cancers are more easily treatable, distant cancers, or cancers that have spread throughout the body, are extremely difficult to treat [14]. In diagnosis, each stage of cancer has unique characteristics that generally become less reversible over time, in time-order from Stage 0 to Stage 4:

Stage 0 is considered the most rudimentary form of cancer mutation. Also called carcinoma in situ, Stage 0 is characterized by the presence of cells with abnormal cell replication sequences, yet it is not technically a cancer yet [10].

After Stage 0, Stage 1 is characterized by localized cancer growth, with little nodal generation [11]. In oncology, node involvement is characterized by the extent to which the lymphatic system (capillaries, vessels, tissue fluid) is redistributed towards a cancerous growth [12]. Because nodes are one of the key indicators of cancerous presence, it is clear that there is little cancerous growth in Stage 1. This information in context suggests that Stage 1 is a relatively treatable form of cancer. In fact, when breast cancer is caught in a localized stage such as Stage 1, it has anywhere from a 98-100% 5-year survival rate, an important indication that catching cancerous mutations up to Stage 1 is a way to keep patients safe [13]. Likewise, non-small cell lung cancer patients who are diagnosed with Stage 1 cancer have a 70-92% 5-year survival rate [15], significantly greater than the survival rate of distant cancer (Stage 4), which is around 6% [14].

As cancerous mutations accumulate, Stage 2 and Stage 3 cancers signify additional nodes and metastasization occurring. Crucially, this decreases the likelihood of survival significantly, as proven by the American Cancer Society [15].

Finally, Stage 4 is the least treatable form of cancer. Stage 4 cancer is characterized by cancerous growths spreading throughout the body, and it is also called metastatic cancer [16]. Stage 4 is the point at which diagnosis is the least useful, and it seems that cancer science should work to diagnose patients well before they reach Stage 4.

While stage-based diagnosis is relatively basic in its standards, other ways exist to diagnose cancer based on time, such as the TNM system, which grades severity of cancer based on tumors, nodes, and metastasis [16]. Regardless of the staging mechanism used, it is clear that the future of cancer science is predicated upon quicker diagnosis coupled with more efficient treatment.

Complexity Matching

One avenue of study that should be explored further is the idea of using critical events and complexity matching to more accurately and quickly diagnose some forms of cancer, such as pancreatic and lung cancers. Historically, the resting heart rate, without external stimuli, has offered a profusion of data on the interactions within the human body. Analysis of crucial events through multifractality can be used to

measure physiological variability, and specific oscillations can indicate certain physiological pathologies [17].

Crucial events are physical manifestations of interactions between units of a network, which often lead to a variable spontaneous ordering process. West found that the waiting time between each theoretical crucial event can be calculated with the equation,

$$\psi(\tau) \propto 1/\tau^\mu$$

where $\psi(\tau)$, the probability density function, has an asymptotic IPL relationship with the time between events, and $\mu < 3$, where $\mu = 3$ implies that a cell is pathological [17].

Using this function and DEA scaling, the formula for survival probability (in relation to damage caused by cancer) of a certain event can be expressed using the formula,

$$\psi(t) = (T/(t + T))^{\mu-1} \exp(-\lambda t),$$

with $2 < \mu < 3$. Grigolini crucially explains in a paper on epilepsy that these parameters for μ are used because the μ of a healthy individual's resting heartbeat is represented by 2, and a diabetic person's resting heart is represented by 3 [19].

By graphing the scaling of crucial events as a function of intermediate asymptotic time, where,

$$\delta = 1/(\mu - 1)$$

it is possible to use a correlation equation to compare the scaling of different individuals to determine whether or not they are pathological for specific conditions, such as diabetes mellitus. This process is called complexity matching.

$$C(t) = (1 - \epsilon^2)\delta_{t,0} + \epsilon^2 \Lambda(t),$$

CORRELATION EQUATION

While these scaling factors are different for different pathologies, there is a general pattern between pathological and healthy individuals; the correlation between each crucial event is lower in individuals

who are pathological. Individuals with higher variance in the correlation equation, signified by Epsilon squared, are generally more pathological.

The public health opportunity presented by the early detection of cancer, as mentioned previously, is tremendous. The sooner diagnosis occurs, generally, the greater the survival rate is of said cancer. Crucially, this shows a large potential for cancer to decrease in severity, if only it were diagnosed earlier. Because analysis of crucial events has proven to be efficient regarding pathologies, as seen in its 95% accuracy index from Gadhoumi '18, it has the potential to be equally as efficient for cancer as it has been for various other pathologies in the past [18]. Because complexity matching can be done as a precursor to Stage 1 disease (as each stage has unique complexities), complexity matching has the ability to significantly increase survival rates of some forms of cancer, specifically those that are deadly even in Stage 1.

Metabolic Dysregulation

One avenue to treat cancer is the use of pharmaceuticals to attack the metabolic dysregulation of genes caused by cancerous mutations. Derbal in 2017 found that the formation of cancer growths (carcinogenesis) causes the dysregulation of metabolism through increased amounts of glycolysis [6].

Specifically, it seems that tumor microenvironments have a large part in metabolic dysregulation. As cancer growths secrete unique cytokines and chemokines, cancer-associated fibroblasts (CAFs) are activated [6]. Consequently, CAFs recycle nutrients back to the tumor microenvironment. Crucially, Fiaschi in 2012 found that when in contact with prostate cancer cells, CAFs alter cell processes using metabolic reprogramming [20]. Specifically, the CAFs gradually make affected cells more dependent on lactate, increasing their affinity towards aerobic metabolism. As dependence on lactate is simultaneously developed with a decrease in the dependence of glucose, cells become gradually more dependent on lactate to drive anabolic pathways such as cell growth. Fiaschi concludes that “cancer cells allocate Warburg metabolism,” a type of specialized, non-aerobic fermentation, to their CAFs, thereby using fibroblast byproducts to replicate rapidly[20]. This metabolic dysregulation thereby creates a mutual state of dependence between cancer cells and their tumor microenvironment.

It seems clear that pharmaceuticals should be utilized in order to disrupt Warburg metabolism, as this should decrease the viability of cancer growths. Derbal asserts that establishing homeostasis, in this case, will in fact turn on a cancer “kill switch,” therefore hindering the ability of cancer cells to rapidly mutate and generate [6]. Specifically, he claims that cancer cells must be denied growth factors, and tissue homeostasis must be restored slowly while avoiding unmanageable reactions. For example, the inhibition of LDHA may reduce lactate levels in tumor microenvironments by limiting cell intake of lactate, thereby driving tumor angiogenesis to a halt while simultaneously limiting the inflammation of tumors and reset cell cycles to homeostasis. The article also notes that drugs targeting other enzymes such as MCT1 and GLUT would reestablish cell homeostasis with respect to cell growth while also limiting angiogenesis and inflammation caused by tumor structure [6]. Ultimately, Derbal identifies drugs that affect NF- χ β , TNF- α , the Jak/Stat pathway, and the TGF- β pathways as potential ways to establish a cancer kill switch, thereby implying that more research must be done in order to establish which drugs may most efficiently limit angiogenesis and reestablish metabolic homeostasis [6].

In addition to the inherent problems present with Warburg metabolism, cytokines and chemokines created by cancer growths help produce tumor macrophages (TAMs), which cover cancer cells, consequently hiding them from the immune system [6]. In fact, it seems that TAMs affect nearly every facet of cancer cell survival [21]. For example, these macrophages promote vascularization, the process of vessel formation, by activating a mechanism called an angiogenic switch, which causes high amounts of vessel formation for nutrient and waste regulation of tumors [21]. Conversely, when TAMs were not present, vessel formation decreased significantly, ultimately helping decrease the likelihood of mutations to accumulate over time [21, 22].

Certain treatments exist to counteract the dangerous effects of TAMs on cancer growths. For example, trabectedin is an alkalizing agent that has been particularly effective in treating sarcomas. Specifically, it blocks the immunosuppressive effects of the macrophages that surround the cancer cells, therefore enabling the immune system to fight against cancerous mutations more actively [23]. Another possible treatment for treating the dangers of tumor-associated macrophages is the use of Colony-Stimulating Factor 1 [24]. This methodology inhibits CSF-1 using inhibitor PLX3397, in doing so significantly

blocking the secretion of cytokines and therefore the ability of tumor macrophages to perpetuate cancer growth. This form of treatment has been attempted in the past, with positive responses on the ability to perform immunotherapy [25]. Ultimately, many methodologies present in literature are aimed at debilitating the effects of tumor-associated macrophages on cancerous growths and mutations. The fact remains that regardless of where cancer rates go in the future, researchers must continue to explore the impact that TAMs treatments can have in curbing the mortality rates associated with cancer.

Conclusion

In this study we have made an attempt to explain cancerous mutations, and explore various future methods to diagnose cancer earlier through statistical analysis. We have shown that the impacts of cancerous mutations can more easily be reversed when cancer is diagnosed early, and discussed various physics-based methodologies that may help catch cancer early. This study is a very general one, and does not represent every potential statistically-based method for diagnosing cancer. However, the article shows that if the oncological community continues to research in the fields mentioned above, there is a way to more efficiently diagnose cancer, and therefore a way to help decrease the mortality rates of cancer. Our future work is to study other types of diagnosis and gauge how they may impact the mortality rates of cancer in the future.

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