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HYPOTHESIS

A Concept of Carcinogenesis as the Consequence of System Decisions Enabled through a Controlled DNA Protection Phenotype

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Abstract. Decades of cancer research have led to the discovery of many contributing factors and progressively more successful treatment approaches. However, a comprehensive model for the root cause of cancer that predicts behaviors in all cases still has not been formulated. Current mutation, microenvironment, and aging based theories on carcinogenesis all tend to regard cancer as a failure of the cellular, tissue, and organ systems. This paper alternatively hypothesizes that cancer can be the intentional byproduct of system decisions to enhance survival and performance during the development of life. To demonstrate the feasibility of this hypothesis, a control mechanism in the form of a DNA protection phenotype is identified based on current cellular and genetic understanding. A conceptual model is then developed to explain carcinogenesis in the context of prioritized protection of gene functions enabled through the control mechanism. Finally, the DNA protection phenotype is used to reinterpret cancer related statistical data. Because carcinogenesis is concluded to be a more controlled process, new treatment strategies leveraging the method of control can be proposed for further investigation.

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1. Background

After decades of intense research, the root cause of cancer continues to elude the scientific and medical communities. A vast array of carcinogens and associated effects in DNA damage has been identified. Hereditary patterns in oncogene expression during carcinogenesis have been discovered. And, susceptibility to cancer due to weakened and aging physical states has been validated. However, these still appear to be merely contributing factors to the formation of cancer as no factor or combination of factors can comprehensively predict cancer dynamics in all people. This lack of total process understanding has caused cancer treatments to remain imprecise even as success rates have improved dramatically in recent years. Current cancer treatments, such as surgery, radiation therapy, chemotherapy, gene therapy, immunotherapy, angiogenesis inhibitor, and hypothermia, tend to often be overly aggressive on the surrounding body and have uncertain effectiveness [1].

In the search for the root cause of cancer, research initially focused on analyzing the physiological characteristics of cancer and statistical patterns in cancer occurrence for select populations. Then, the ability to decode the DNA and the discovery of mutations in cancer cells brought the center of gravity in cancer research to genetics and molecular biology. In recent years, there is also growing emphasis on studying cancer not merely as the failure of single cells but as the consequence of entire cellular environments. These three major paths of research are briefly summarized below. So far, the research has been very topic focused and sometimes competitive between the different paths. This creates an opportunity for more integrated reinterpretation of current research results.

1.1. Researching the Root Cause of Cancer through Modeling Cellular Mutations

Since the discovery of chromosomal aberrations due to accumulated gene mutations in cancer cells, the theory of somatic evolution as the root cause of carcinogenesis has dominated cancer research [2]. Somatic evolution proposes that, as a colony of cells randomly experience DNA alterations and translocations due to carcinogens and inherent instabilities, those cells which gained advantages in mutated gene expression and function will start to survive longer while other cells die off. As gene expression is continuously shifted by carcinogens, the surviving cells will assume cancer characteristics as part of their fitness criteria [3].

Mutation research has a long historical lineage [4]. Based on experimental results in genetics, carcinogenesis is now popularly understood as a long sequence of cellular shifts that include: 1) sequential mutations that evade apoptosis, 2) self-sufficiency in growth signals, 3) insensitivity to anti-growth signals, 4) tissue invasion via metastasis, 5) limitless replicative potential, and 6) sustained angiogenesis [5]. Cancer research into the causality of these shifts has focused on cellular sloppiness and poor adaptation, and cancer is popularly viewed as a disease of cellular decision mistakes in G1 phase [6]. However, even with the activation of oncogenes to cause accelerate activities, compromise of stability genes to launch the mutator phenotype, and the creation of wild type tumor suppressors [7], it is still debatable as to how a cell can undergo such severe chromosomal aberrations as seen in cancer without total system collapse [8]. Nevertheless, genetic testing as a form of cancer prevention and treatment among the general population is starting to increase [9].

Current research regarding mutations and gene expression leading to cancer is focused on understanding the DNA damage response phenotype. Areas of research include the signaling of double strand breaks via ATM, CHK2, and other protein activation pathways; the control of cellular and intercellular responses via p53 and related protein prosphorylation

patterns; specific countermeasure actions such as free radical clean-up, cell phase arrests, and signal transduction; and specific decisions such as recombination for recovery, terminal differentiation / early senescence, and apoptosis [10]. Vast quantities of data have been gathered through molecular biology techniques, and incremental advances in understanding gene expression are continuously being made [11].

In recent years, a branch of mutation research has focused on the hypothesis of cancer starting from stem cells instead of normal somatic cells [12]. Because gene taxonomy and cellular phylogeny leading to capabilities that would cause a cell to reach a cancerous state must be challengingly complex [13], the flexibility and instability of stem cells would in part explain how this complexity can be achieved. The growth advantage of stem cells could explain why cancers form despite continuous cellular efforts to halt tumor progression even after the failure of tumor suppression genes [14]. However, results on the role of stem cells in carcinogenesis are still inconclusive, and some results have yielded doubts about this branch of research [15].

1.2. Researching the Root Cause of Cancer through Modeling Tissue Organization Fields

The complexity of the cell has been long recognized [16], and some gene expression researchers continue to question the adequacy of biological determinism and reductionism [17]. Since the 1960s, a number of scientists have adopted the counter view that all the elements and relations associated with carcinogenesis are far from being understood because of the complexity of organic systems and how cancers are connected with this complexity. At the macro-level, it has been pointed out that the entire physical and mental state of cancer patients, which includes many poorly defined factors, plays a role in the progression of the disease and treatment successfulness. At the element level, it has been pointed out that there is great nonlinearity between gene expression and phenotypes leading to relations that are far more complex and dynamic than previously assumed [18].

The dominant theory challenging somatic evolution argues that the root cause of carcinogenesis lies more in the tissue organization of environments where cancer cells form [19]. Specifically, cells can work together as a group to prevent cancer formation or the environment of the group can be shifted to encourage cancer. The role of the microenvironment across regions of cells in carcinogenesis is an expanding area of research [20]. Results have already shown that cells with mutated p53 transcription factor proteins are four times more likely to induce cancer when transplanted into a microenvironment where the surrounding cells have been inflamed / disrupted by irradiation. Based upon these recent results, the tissue organization field theory has become a strong second path of cancer research [21].

1.3. Researching the Root Cause of Cancer through Statistical Modeling of Organic Processes

Finally, the limitations of molecular biology have encouraged some researchers to continue studying the physical and statistical characteristics of cancer occurrence. The strong association of carcinogenesis with aging continues to yield more theories [22] and improvements in mathematical modeling capability have permitted evolutionary biologists to study how evolution rates impact genetic instability [23]. The goal of such research is to discover hidden organic processes and latent factors in carcinogenesis that may or may not be due to genetic anomalies. Given advances in data mining and the recent introduction of systems analysis techniques to the biological sciences, the discovery of new mechanisms merits continued consideration [24].

2. A New Hypothesis for Carcinogenesis

Examining the current paths in cancer research as described, there is a common tendency to view cancer as a flaw of the system at the cellular, tissue, and organ levels. Yet, such a view has not yielded a comprehensive explanation of cancer or an integration of research results. One can alternatively hypothesize that cancer is an intentional byproduct of critical developmental decisions during evolution to optimize survival and performance for the species and eukaryotic life in general. Had the cellular, tissue, and organ systems not developed in a way that allowed for carcinogenesis, the consequences would have been worst for life. This hypothesis suggests that the process of cancer formation might have more control mechanisms than currently assumed and that such yet to be identified mechanisms could provide better integrated understanding of currently disconnected research results. Even though the proposal of more control mechanisms is somewhat divergent from the current paths of cancer research, the evaluation will show that this hypothesis is still consistent and potentially complementary with the mutation, tissue, and evolution based theories on cancer.

Critical developmental decisions and control mechanisms that enable these decisions is a rational consideration because life developed under thousands of threats to the DNA. Today, we call these threats carcinogens because the developmental decisions were made correctly. However, the real nature of these threats was to challenge the success of life itself. In today's life, carcinogens are eliminated in the intercellular and intracellular environment of eukaryotic organisms by specialized organs such as the lymphatic systems and cell functions such as free radical clean-up by specialized proteins. Other carcinogens are blocked by the cell membrane and cellular compounds such as melanin and anthocyanin that absorbs UV radiation. Then, the effects of carcinogens are addressed by the DNA damage response phenotype. Yet, none of these known mechanisms can control the nature of cell and organ systems in response to threats.

If one sees carcinogens as all individual attacks upon the cell, then one might easily conclude that there is no way for the cell to control the consequences of attacks. DNA damage must be random, and development emphasis must be on better damage response. However, the thousands of carcinogens can be grouped into three types of threats based on how they interact with the cell:

- *Linear path threats* - consist of photonic energy absorption in the ultraviolet (UV) regime, ionization tracks caused by high energy nuclear particles, ionization tracks caused by X-ray to gamma ray released fast electrons, and microzones of path associated free radicals caused by collateral ionizations.
- *Fluidic motion threats* - consist of all manner of mutagenic compounds such as peroxides, psoralens, and free radicals that enter the cell or are produced within the cell that rely upon microfluidic motion to reach and react with the DNA molecule.
- *DNA honing threats* - consist of retroviruses and enzymes such as RAG1 and RAG2 that can directly target select sections of DNA molecules.

As the level of exposure to different carcinogens has changed over millions of years, these three threat types with different paths of attack have remained. This consistency of threat types gives life adequate time and focal points to develop control mechanisms. The identification of control mechanisms in responding to different threats would validate the hypothesis that life systems are much less flawed then currently assumed. Then, the understanding of these control mechanisms could advance cancer treatment approaches.

3. Evaluation of the Hypothesis

In the evaluation of this hypothesis, genetic and cellular dynamic understanding will be used

to show that a DNA protection phenotype could exist to support the control of cellular development under the three types of threat. Then, this newly proposed phenotype can be placed into a conceptual model of how cells, tissue, and organs developed as complex systems to support life at the expense of allowing for cancer. Finally, the presence of this control mechanism can introduce ways to reinterpret data on the statistical occurrences of cancer. This evaluation does not proclaim to prove the hypothesis or identify all of the control mechanisms that might exist. It does, however, show that the hypothesis is consistent and integrative of current research results and thus merits further consideration by the scientific and medical communities.

3.1. DNA Protection Phenotype as a Control Mechanism Associated with Carcinogenesis

Current studies into the complex multilayered structure of chromosomes have focused more on gene expressions to enable known cell and intracellular processes. However, the structure of chromosomes also inherently provides levels of protection to the DNA strands. DNA, which is composed of purine and pyrimdine bases held together by a backbone of phosphate and sugar, can be damaged by carcinogens to result in mutations and translocations of the genes they enable. However, the positioning of gene sequences within the structure of chromosomes automatically varies their level of exposure to different threats. If cellular development in the advancement of life positioned genes for both protection and optimal expression, then there is a clear control mechanism for how decisions can be made to protect core genes and gene functions at the expense of damage to other gene segments.

The existence of this DNA protection phenotype would explain why organisms seeking to block cancer cannot simply achieve a final failsafe state where all consequences of accumulated chromosomal aberrations result in cell death. DNA repair capability could have evolved to be the first mechanism that fails under excessive mutation to enable cell death, and other system failure modes could have evolved in the chromosomal structures to guarantee cell death under aggressive cancer processes. But, if the cell had already made a developmental decision regarding when to permit cancer through controls such as DNA protection, then the notion of a final failsafe in system operations would be a contradiction.

Research results showing that mutations in genes do not occur randomly support the notion of selective DNA protection [25]. Some genes are more prone to mutations than others even under broadly distributed threats to the entire chromosome. At the DNA level, double strand breaks also do not occur randomly but instead in clusters of segment lengths [26] [27]. Based on these indicators, we are encouraged to press forward in figuring out how protection processes can fit in with the still not fully elucidated processes of DNA damage detection and response [28].

3.1.1. Why DNA Protection Could Exist

It has been long accepted that the 10,000 fold packing of the DNA around histone structures offers an intrinsic level of passive protection against environmental threats [29]. Further, gene segments in different parts of the supercoiling configuration of the DNA molecule will be exposed to different levels of threat [30]. To elaborate on the inherit protection offered in supercoiling, it is important to note that the 2nm DNA strand of a chromosome, which stretches to tens of centimeters in length, yields immense exposure to all three threat types if unprotected. Even a bundling of the DNA into tighter structures would offer minimal added advantage over penetrating radiation and the bundling will most likely hinder gene expression. Thus, the known contribution of the histone structures in absorbing some level of

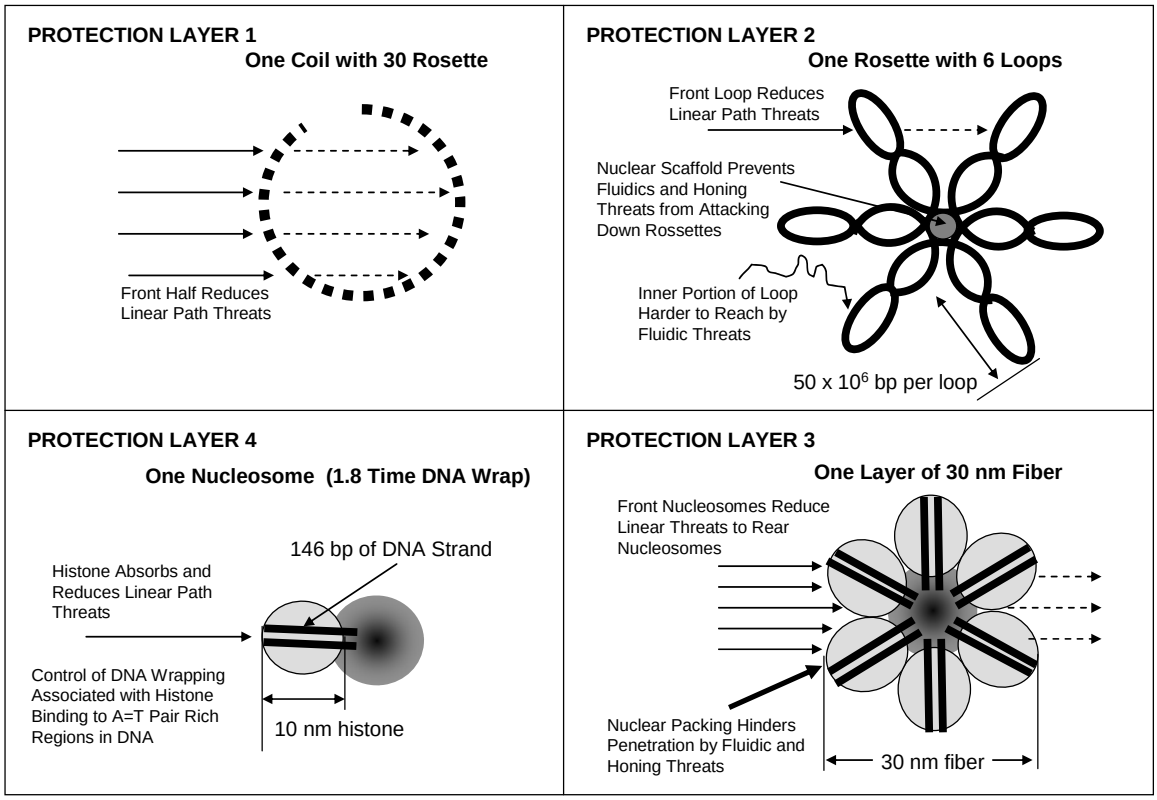

Figure 1. **Layers of Protection Offered in Supercoiling.**

radiation and in blocking fluidic and honing threats from getting into inner parts of the coiling structure does play a role in the protection of select gene segments from additional damage.

The key question given this known capability to passively protect is whether genes are located across the chromosomal structure without consideration of their importance or whether functional priority is a factor in gene placement? If the latter case is true, then there is a hidden DNA protection phenotype that is hard to quantify because protein activity may not be involved. Instead, genes have to be mapped to the functional levels and their positions have to be mapped to the relative quality of shielding, avoidance, blocking, and hardening. This correlation can be achieved in a deterministic manner. And, as the pattern of gene location based on the protection phenotype is better understood, the functional association of newly discovered genes can be projected simply based on where they are located. If gene location is a factor of both protection needs and expression needs, then the patterns of the protection phenotype will be harder to filter out.

FIG 1 shows how truly effective the protection offered by histone structures can be in the process of supercoiling. Each level of coiling offers additional protection, and all levels of coiling offer a layered protection approach for linear path threats. Since linear path radiation threats are all based on particle density in the engaging wavefront, individual particle energy, and the wavelength of the radiation, the primary defense against this threat when particles cannot be reflected away is the absorption of particles by less important elements of the cell. In the case of DNA protection, every particle that is absorbed by the histone structure is a statistical reduction of threat for DNA segments behind the histone. Thus, the most protected DNA

segment from linear path threats are those behind layers and layers of histones achieved in supercoiling. The ways linear threats can overwhelm such histone shielding are by high dose attacks and high energy attacks. A high dose attack by photonic ionizing radiation in the x-ray to gamma-ray regime can be either by a high intensity wave or a long duration wave. Either way, the absorption offered by histone shielding is insufficient to reduce photonic penetration and damage to acceptable levels. A high energy attack by densely ionizing radiation can be by any type of heavy particle that collides with cellular molecules. These particles are hard to stop by energy elimination through absorption or scatter and the histone shielding will have minimal effect [31].

At the rosette and 30 nm fiber levels, the configuration makes it hard for fluidic threats and even honing threats to reach select segments of the DNA. The extension of the loop out from the rosette like fins inherently increases the probability of mutagenic compounds hitting the outer regions of the loop via fluidic motion. This decreases the fluidic threat to DNA segments near the nuclear scaffold. At the 30 nm fiber level, the packing of the histone dominant nucleosomes blocks both fluidic and honing threats from reaching the center of the fiber. The blocking also reduces the amount of fluidic material around the center of the fiber. With less fluidic material around select DNA segments, the creation of free radicals from tracks of ionizing radiation is further hindered.

3.1.2. How Could the DNA Protection Phenotype Work

In order for the cell to prioritize the protection of gene segments, two mechanisms must exist. First, the cell must have the ability control the binding of DNA to select histones. Second, the cell must have the ability to generate segments of DNA that can be damaged/mutated with little impact to critical gene expression. Current research results seem to indicate that the cell may have these two mechanisms.

In the case of binding control, experiments reveal that A=T based pair rich regions of the DNA promotes binding to histones and so a selective placement of A=T clusters might yield a control mechanism [32]. Recent gene expression research provides more convincing results [33]. Specifically, the research is showing that gene expression is highly dependent on varying characteristics in the histone structure [34]. This selective association between gene and histone strongly suggests that some form of control mechanism could exist. Investigations into histone modifications as a form of transcriptional regulations are increasing [35]. One major discovery is the identification of K27 and K4 tagging sites on chromatin structures to control the access of genes for cell specialization [36]. This functionality of tightening and loosening of DNA strands around the histones was revealed through the characterization of bivalent states for sites in embryonic stem cells and the loss of simultaneous K27 and K4 tagging as cells specialize. In specialized cells, suppressed genes no longer have to be ready to spring into activity. The required precision of such tagging by polycomb protein complexes to control DNA binding to histones for cell specialization is perhaps the strongest indirect evidence so far for the cellular capability to use histone in DNA protection. The evidence of histone as a reference frame is increasing [37]. In fact, there may even be real-time active mechanisms in the protection phenotype where vulnerable segments are bound tighter and shielded better when threats are realized. What new research can focus on is the specific association of the histone reference frame and binding control proteins with DNA positioning and tightening for protection.

In the case of DNA segments that are anticipated to receive damage, the fact that more than 95% of the DNA strand consists of non-gene coding introns leads to the consideration that not all the introns can be just for regulating gene expression. The range of lengths for introns, from 50 bp to 20,000 bp, gives intron

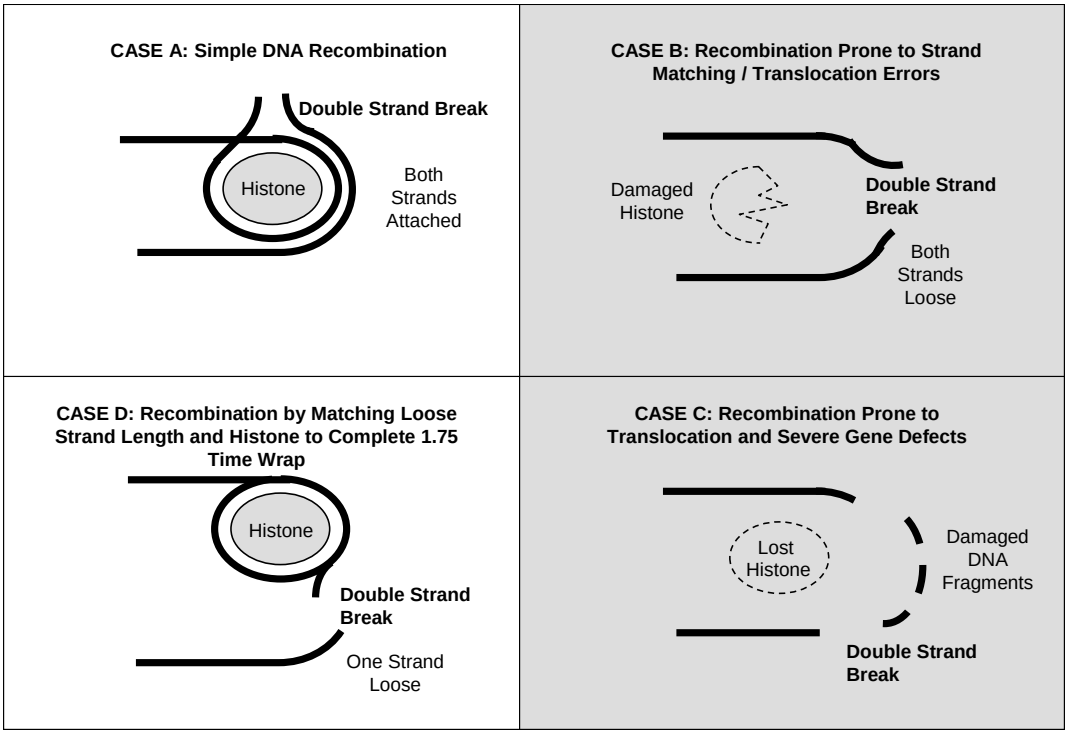

Figure 2. **Potential role of histone reference frame in rapid damage response.**

segments the ability to position a critical DNA segment from only half a histone to a whole side of the 30 nm fiber and to a different region of the rosette loop in the course of chromosomal formation. The less than 1000 bp length of most exons creates a fine level of gene code compartmentalization that is ideal for intron positioning. Upto 600 bp can be hidden behind a 30 nm fiber. And, an entire gene can be spread out or compacted along a rosette loop to satisfy unique protection and expression needs. The fact that histone genes do not have introns further supports this concept of DNA protection because genes for the creation of histones must pre-date intron utilization in eukaryotic organisms in order for this capability to form. The slow process of cellular development through chromosomal change hinders our ability to demonstrate cause and effect in DNA protection. However, data mining and pattern analysis of large quantities of genetic data cold help us identify possible outcomes of past developmental decision on what to protect.

The existence of a DNA protection phenotype based on functional priorities in gene expression would mean that there must be a coupling between protection and the DNA damage response phenotype. For example, accurate protection activities at the histone level should have some correlation with accurate repair activities to prevent alterations and translocations. The persistence of the repair function even after higher cell functions have been degraded due to the failure of total damage response suggest that DNA repair and DNA protection may have been prioritized similarly in the development of cells in eukaryotic life. Therefore, it is worth considering that DNA repair will use the same histone reference frame proposed for achieving precise protection.

FIG 2 shows four cases that reveal the potential benefits of histones in DNA repair. In Case A, the recombination of DNA for when both strands are still attached to the histone is a simple process. The identification of H2AX phosphorylation at the tips of double strand

breaks then explains how the two ends are again matched up and fused [38].

In contrast, the recombination of DNA for when the histone structure is damaged, as shown in Case B, or when histones are lost due to extensive short track DNA damage, as shown in Case C, is fraught with possible errors. Without a reference frame, there are no inherent ways for a non-homogolous repair process to validate the matching of two strand ends. The cell could in theory uniquely tag both ends of a strand break immediate upon occurrence, but such a complex mechanism does not appear to exist based on the level of translocation and chromosomal aberration errors observed.

A frequent situation in DNA double strand breaks, however, is when strands are separated but there is no damage to the histone, as shown in Case D. In such cases, the 1.75 time wrap of the DNA around a histone is a very good number for promoting one end of a broken strand to remain attached to the histone from a biomechanics perspective. Further, the number, which is below 2.0 times wrap, eliminates most potential ambiguities when matching the free strand end to the histone attached end. The odds are low that two double strand breaks will occur at the same point in the 1.75 time wrap and be close enough to one another to cause a mismatch. The ability to use the histone as a recombination reference requires the same level of precision in DNA to histone relations as that needed to enable protection mechanisms. Therefore, if experiments can show that this last condition does have much higher successful recombination rates than when histones are damaged, the concept of a DNA protection phenotype is again supported.

3.2. A Conceptual Model of Carcinogenesis Based on DNA Protection

Advances in complex systems research is showing the natural systems are far more self organizing and adapting than previously believed [39]. Therefore, the notion that the development of cells, tissue, and organs could have incorporated a series of precise decisions on protecting gene functions to enhance survival and performance at the cost of cancer is becoming more plausible.

In a model of carcinogenesis based on DNA protection as the control mechanism, the cell would possess cancer behavioral characteristics as a part of core functions in gene expression. These functions would be constrained by higher order functions in eukaryotic organisms, but they would not be a result of evolution through randomly acquired gene behavioral abnormalities. The eukaryotic cell's ability to survive can be seen when a few cells among thousands can still manage to sustain operability even after exposure to 1600 rads of X-ray radiation. This ability is innate to the cell and not due to cancer acquired capabilities. Further, the theory that organisms in an era of pre-Darwin life where able to share genes without species barriers [40], suggests that even primitive cells are quite effective at controlling DNA strand breaks and strand fusion. While eukaryotic cells do not have restriction enzymes, the presence of ligase enzymes and the cell capability of recombining rough double strand breaks by means of blunt end legation or inserting short repeat sequences show in part how comfortable the cell can be at handling breaks at the end of genes and in the middle of genes [41]. Therefore, the first imperative for eukaryotic life may still be the survival of individual cells, because one living cell can restart life even when the total organism has died.

Considering the cell and the cell environment as a complex system, several levels of core functions can be hypothesized based on what is most important to the totality of life. If the cell can protect these core functions, it would prioritize the protection based on the following sequence of levels as deduced through systems operations theory. The inability of the proposed DNA protection phenotype to offer equal protection to all genes means that genes at Level 1 will get the highest protection and then the

protection will drop as the levels increase. Because the prioritization goes from the most basic functions to the more sophisticated functions in eukaryotic organism, the complete set of functional control will often exist at higher levels and be less protected. Therefore, it is the corruption of functional controls while the functions are still effective that gives rise to tumor and cancer behaviors.

Protection level 1 (core function of absolute survival): Gene expressions that enable the cell to sustain operations under extreme damages and adverse conditions.

Protection level 2 (core function of intercellular position shifts): Gene expressions that enable the cell to realign itself within a colony of other cells to change the organization of the colony.

Protection level 3 (core function of intercellular collaboration): Gene expressions that enable signal transduction and other mechanisms to allow a colony of cells to work together as a whole.

Protection level 4 (core function of intercellular position awareness): Gene expressions and cellular tags that enable the cell to identify its location relative to other cells in a structure.

Protection level 5 (core function of cell specialization): Gene expressions that enable cells to assume different characteristics and capabilities within a single organism.

Protection level 6 (core function of cell senescence): Gene expressions that enable organisms to retire aging cells after set number of divisions.

Protection level 7 (core function of cell apoptosis): Gene expressions that enable organisms to terminate malfunctioning cells.

The potential existence of these protection levels implies that cancer research cannot just focus on the cellular barriers against mutation, tumor formation, and cancer formation. A great deal more grouping of changes in cell functions could be occurring in between these major transition points. Figure 3 integrates the major barriers / transition points with the protection levels. Tumor and cancer formation can then be understood as the defeat of protection levels by threat to the DNA. The first barrier is the DNA damage response phenotype, which ranges from DNA repair to induced apoptosis. Once errors in DNA repair are allowed to accumulate to affect gene functions, this barrier is breached and functional degradation will start. The degrading of apoptosis capability once level 7 gene expressions begin to fail allows chromosomal aberrations to progress. However, this is still less important than senescence because the consequences of cell malfunction might still be mitigateable through senescence, immune response, and containment by surrounding cells. The degrading of senescence capability allows telomerase expression to restart [42] and eliminates the telomere shortening trigger for apoptosis [43]. However, this is still less important than cell specialization because broken immortal cells can still perform functions useful to the organism. Once cell specialization capability is degraded, observable abnormalities will begin to emerge. But, growth rates can still be constrained as long as the deformed cell knows its position relative to the totality of the organism.

This conceptual model suggests that there are several levels of cell state identifiable through gene expression changes prior to the next barrier against tumor growth. Research shows that all tumors have evaded apoptosis, 85% of tumors have evaded senescence, and all tumors have distorted cell specificity [44]. By the point of cancer, senescence has also completely failed. The barrier against tumor growth is currently identified as the immunoediting process where the immune system can destroy abnormal cells with instruments such as killer T cells and macrophages [45]. The effectiveness of the immune system in preventing cancer and the earliest point of immune response against cell abnormalities are areas of increasing research.

As DNA alterations and translocations continue to mount to degrade a cell's theorized position awareness capability [46], cells would be allowed to grow as if it is not a part of the

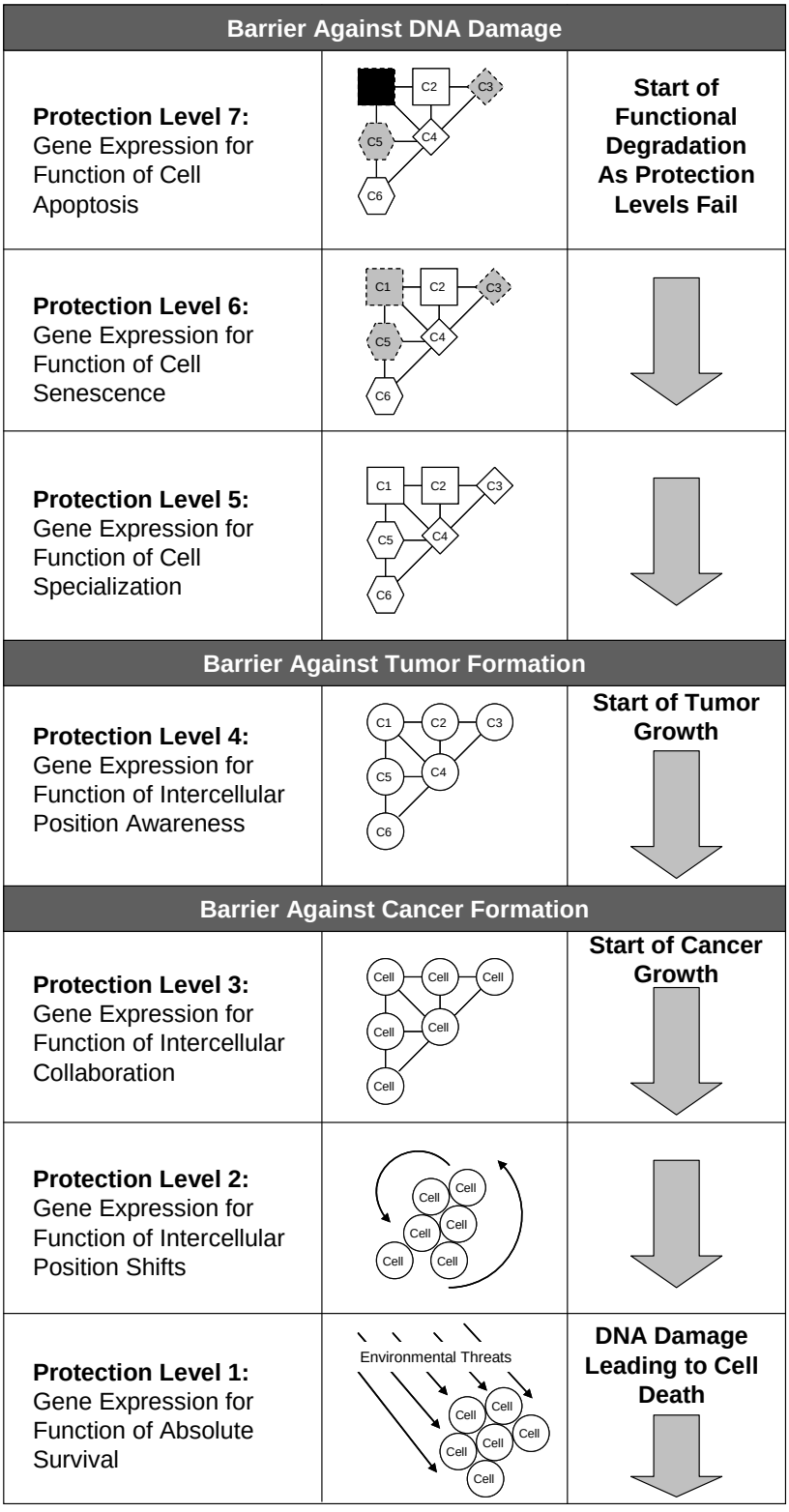

Figure 3. **The pattern of functional degradation in cell experiencing DNA damage.**

TABLE 1. Current treatment types based on cancer characteristics.

Observable end state cancer characteristics	Treatment type	Mechanism
Cancer cells have severely altered DNA structures and reduced damage repair capability	Radiation Therapy	▪ Use ionizing radiation (X-ray, gamma ray, particle beams) to damage cancer cells' DNA to the point of inoperability
Cancer cells replicate through cell division more frequently than most other adult cells	Chemotherapy, Photodynamic Therapy	▪ Use chemicals to kill cells during the cell division process ▪ Use light activated chemicals to kill cells in specific locations
Cancer and tumor cells have noticeable physical deformities and primary growth region	Surgery, Cryosurgery, Laser Therapy, Gamma Knife, Proton Therapy	▪ Physical removal of cancer regions ▪ Kill cancer cells by freezing ▪ Kill cancer cells by surface or internal heating
Cancer and tumor cells have weaker heat transfer / management capability	Hypothermia	▪ Increase thermo loads in cancerous region to point where normal cells can still manage while cancer cells die
Cancer cells require angiogenesis to grow	Angiogenesis Inhibitor	▪ Agents that block the increase of blood supply to cancer cells
Cancer cells have recognizable markers for triggering immune response	Immunotherapy	▪ Agents such as injected antibodies and cytokines that can trigger immune response and / or increase the intensity of response
Cancer cells have common genetic characteristics or triggers	Gene therapy	▪ Use of vectors such as viruses to place apoptosis inducing suicide genes or to replace gene triggers

organism and become a tumor. This loss of awareness also permits tumor cells and cancer cells to grow in other parts of the body through metastasis. However, this is still less important than the capability to collaborate because neighboring cells can help to stabilize even a large group of malfunctioning cells. This suggests that the microenvironment is the next barrier that prevents tumor cells from becoming cancer cells. The protection offered to the cells functional capability to operate in microenvironment to form tissue creates a bridge between the mutation and tissue theories on cancer.

Cancer cells will emerge once intercellular collaboration capability is degraded. Yet, collaboration is still less important than the capability for cells to shift positions and survive under stress as these are the base functions of eukaryotic life when organisms are being formed from embryonic stem cells. Since adult stem cells also exhibit more activity at the basic functional levels, one can speculate that they may be harder to protect and thus more vulnerable to carcinogenesis. This increased vulnerability may lend some credence to the stem cell theory of

cancer, but cannot show that cancer only comes from stem cells.

Finally, the DNA of cancer cells can be further damaged to the failure of the absolute survival function. At that point, the cancer cell will experience operational death.

This conceptual model is proposed as a new starting point for investigating cancer, and it is anticipated that future research will adjust current assumptions, validate the approach, and refine the accuracy of the model. Also, the proposed prioritization of gene functions does not imply that one level of genes must fail before lower levels can suffer damage. Instead, the priority is simply reflected in the statistical pattern of failure due to differential degrees of protection. This model does expand upon the mutation theory of cancer by suggesting that oncogene activation in carcinogenesis is an observable manifestation of suppressed gene functions at the lower levels once higher level functions have been degraded.

3.3. Reinterpretations of Cancer Related Data Based on Controlled DNA Protection

The presence of the DNA protection phenotype and a model for carcinogenesis based on prioritized DNA protection should yield unique characteristics in the patterns of cancer occurrence and cell survival under threats to the DNA. If we look at mammalian cell survival curves under different forms of ionizing radiation, there is a clear linear relationship between cell death rate on a logarithmic scale and radiation dosage when densely ionizing radiation is applied. Cell survival rate steadily drops to below 0.1% at 400 Rads of radiation exposure. This relationship can be interpreted as all the DNA protection methods being ineffective because densely ionizing radiation will penetrate all cellular and chromosome level barriers. Given the observed severity of the damaged lesions under this form of attack, even DNA damage response appears to be marginally effective.

In contrast, the curve for mammalian cell exposure to photonic ionizing radiation shows a slow decline in cell survival up to 800 Rads and then a rapid decline until survival rate drops to nearly 0.1% after 1600 Rads [47]. This shoulder in the curve has spawned many theories, but a clear process explanation has yet to be well elucidated. Given the proposed DNA protection phenotype, this shift in decline of cell survival rate can be explained as the protection methods still being partially effective until accumulated damage caused by 800 Rad has been reached. Then, only the DNA response phenotype continues to work in some cases until all the cells are dead. The shoulder in the curve strongly suggests that at least two forces are work. At the chromosome level, what may be happening is that protection fails once the histone structure can no longer be effective reference frame when saturated and disrupted by radiation. However, DNA repair will continue on under higher radiation levels until all cells die.

The interpretation of DNA protection failing under accumulated radiation damage can be expanded to the idea of DNA protection failing under accumulated chromosomal damage in general. This would explain why the odds of cancer does not increase linearly with age but instead escalates rapidly towards the final decades of life. Since people are exposed to carcinogens in a somewhat linear manner over time, the rapid increase in cancer for the elderly can be investigated as a sudden weakening of DNA damage response or failed DNA protection with continued damage response. The determination of which process fit better with actual cancer occurrence curves needs to be achieved through further research.

The age of genetics has reduced emphasis on statistical studies into cancer patterns in cells and the human population. The potential for latent patterns associated with a controlled protection based model of carcinogenesis encourages statistical research to be reinvigorated.

4. Consequences of the Hypothesis

The concept of carcinogenesis being a more controlled occurrence in the cell due to priorities in DNA protection shifts the philosophical emphasis in cancer treatment. Instead of think of about each case of cancer as a unique situation resulting from random mutations, we can start to explore treatments that address the more orderly process of cancer formation.

The assumption of chaos has guided current cancer treatment strategies to focus on the end state characteristics of cancer as well as starting point vulnerabilities such as hereditary factors, overall health, and exposure to carcinogens. The observable characteristics that distinguish a cancer cell from a normal cell are identified in TABLE 1. For every characteristic, there are treatment types that leverage that difference [48].

The challenge with focusing on end state characteristics is that the delineations between cancer cells and normal cells are not always precise. For example, identifying the right radiation level and type to kill all cancer cells while allowing normal cells to recover is difficult and chemicals that kill cancer cells will also kill specific types of healthy cells that are undergoing more frequent division. Even in the case of direct procedures on cancer growth, a small percentage of cancer cases do not have a primary growth region prior to metastasis and the observable boundary between cancer cells and surrounding healthy cells may not always be clear. As a result, current cancer treatments must trade-off between not completely eradicating the cancer and doing too much harm to the rest of the body.

If we now shift to the proposed process of controlled cell failure in carcinogenesis, then there is the potential to treat cancer by impacting the functional degradation. One form of impact is to degrade cancer cells further to the point of operational failure. The mechanism of radiation therapy may actually be to damage DNA to the point where the core function of absolute survival is wiped-out. Therefore, treating cancer with carcinogens is not totally a new idea. This hypothesis suggests that other carcinogens might also have the ability to knock out the survival function if applied correctly. The notion that cancer cells are actually quite operationally weak despite their aggressive nature is counter intuitive to the concept of somatic evolution but not to the concept of controlled failure. The application of carcinogens to cancer cells or cells on the path to cancer might also change functional characteristics such as: 1) sensitivity to the immune system, 2) distinctiveness to enable identification and removable, 3) vulnerability to heat and cold, and 4) metabolic susceptibility to chemicals. To achieve characteristics that are more favorable for cancer treatment, the patterns of functional degradation must be better understood. Then, the mixture of carcinogens, the sequence / timing of application, and rate profile of application can all be investigated as to how the degradation patterns can be modified.

Exposure to carcinogens prior to the degradation of cells should obviously be avoided as a means of DNA damage prevention. However, once massive exposure to carcinogens leading to cancer has already occurred or if continuous exposure cannot be avoided, shifting the patterns of failure could make sense. Cancer could be a disease of cellular and organism imbalance against carcinogens. For different conditions of exposure to carcinogens, there seems to be people who can resist the onset of cancer. In these people, the carcinogens may only be degrading cells in a pattern that can be handled by DNA damage response, immune response, and / or the microenvironment. Cells that would have become cancerous might instead be rapidly falling to the non-operational state. Therefore, people who have never developed cancer may also merit further study as a part of alternative avenues of research introduced through the hypothesis of controlled carcinogenesis.

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