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Review Article

Cancer is a Genetically Modified Organism Hypothesis

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Abstract

During DNA replication, if the DNA strand breaks, such as a Double Strand Break (DSB), either the exogenous viruses or endogenous viral relics may be incorporated into the newly replicated cell. The new cell is a Genetically Modified Organism (GMO) due to these viral genes. The GMO cell will express the trait of the gene which it arose from, known as proliferation, a trait of the unicellular organism. The new genetically engineered cell is a viral gene cancer (VGC). It flouts the normal cell's standard rules of growth and it has a chaotic DNA replication. The other viral genes may be integrated into the new cell by Horizontal Gene Transfer (HGT).

As the cancer progresses further, the ancient genes which were deeply imbedded into the mammalian genome may be incorporated into new GMOs by HGT. The new cell, an Ancient Gene Cancer (AGC), would express the traits of the genes from which it arose. Its traits are proliferation, lost adhesiveness and stiffness, and anaerobic metabolism. This is because the ancient eukaryotic cells lived in water and in a hypoxic environment. The AGC could break off from the tumour and enter the blood vessel because of the lack of the cell's adhesiveness. With less stiffness, the AGC could deform itself and squeeze through a tiny intercellular gap. This is the reason the AGC could metastasize into other organs.

Keywords: Viral gene cancer; Ancient gene cancer; Hallmarks of cancer; Cancer is GMO; Cancer hypothesis; Cancer theory

Abbreviations

DSB: Double Strand Break; GOE: Great Oxygenation Event; HGT: Horizontal Gene Transfer; GMO: Genetically Modified Organism; VGC: Viral Gene Cancer; AGC: Ancient Gene Cancer; ERV: Endogenous Retroviruses

Evolutionary Background

The early life of Earth consisted of viruses, bacteria, prokaryotes and eukaryotes, etc., which emerged during this primordial time. There were many genes exchanged among these unicellular organisms. These unicellular organisms were selfish [1]. No free oxygen existed in early Earth time until about 2.7 billion years ago when cyanobacteria began producing oxygen and glucose by photosynthesis. Any oxygen they produced was chemically captured by dissolved iron or organic matter. The eukaryotic cells lived in water in a hypoxic environment and metabolized glucose by fermentation. These organisms were unable to live on land because there was no ozone layer protection from the Sun's ultraviolet radiation. These anaerobic metabolism organisms lived in a harsh environment and they have stronger innate immunity. The Great Oxygenation Event (GOE) happened about a half-a-billion years ago when the oxygen sinks became saturated.

Many new species evolved after the GOE with aerobic metabolism. Aerobic metabolism is 19 times more efficient than anaerobic metabolism; therefore more complex species evolved and created biological diversification. The anaerobic metabolism organisms were either massively extinguished or evolved into aerobic metabolism organisms. Viruses have invaded mammals or their ancestors, and viral genetic relics have been left in the host's genome. The mammalian genome has both genetic relics of aerobic metabolism viruses and ancient eukaryotes genes.

DNA Replication

There are roughly 32.7 trillion cells in the average adult human body. If the mammalian cell becomes old or damaged, the cell is replaced by replicated cells. During each cell division, more than 3.3 billion base pairs of genomic DNA have to be duplicated. Defects can possibly arise when DNA is copied during cell division. There would be disastrous consequences if sufficient defects were accumulated. Therefore the normal cells have a finite number of replications, referenced by shortening the telomeres, in order to avoid a possible unmanageable quantity of mutations being accumulated. In Khoronenkova's study, about 10 to 20 thousand endogenous DNA Single-Strand Breaks (SSB) form per day and 10-20 DNA Double-Strand Breaks (DSB) are formed during this period. These errors could lead to disease, including cancer [2].

Repair of the Defective Cell

Elephants have a 100 times more cells than humans, yet their cancer mortality rate is less than 5 percent compared to 11 to 25 percent in humans. In the African elephant genome there are at least 40 copies of genes that code for protein p53 compared to only the two found in humans. Elephants increase their apoptotic response following DNA damage, rather than relying on the immune system to mop up the defective cells after the cell is replicated [3]. In Abrams study, the normal p53 gene action restrains transposons that can make copies of themselves and move to different positions on chromosomes [4]. The Nobel Prize in Chemistry 2015 was awarded to three pioneering scientists of DNA repair. Tomas Lindahl demonstrated base excision

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repair, which constantly counteracts the collapse of our DNA. Aziz Sancar has mapped nucleotide excision repair. Paul Modrich has demonstrated mismatch repair, reducing the error frequency during DNA replication by about a thousand-fold [5].

Defective cells evade eradication by checkpoints

Mammals may ignore the cancer cells and think they are non-foreign cells. Some examples are as follows:

- Walsh states that the mother's immune system does not reject the foetus inside the mother's placenta. Although the foetus has half the mother's genes, it also has half the father's genes. For the surrogate mother, the foetal genes are completely foreign genes. The foetus obtains nutrients from the surrogate mother by creating new blood vessels. The immune system, however, does not reject the foetus inside the placenta. Cancer cells may possess a similar ability, creating a shield of "don't eat me" to avoid attack by the immune system [6].

- In Ngo's study, the mice model of melanoma blocked the cell surface proteins CD47 in combination with CD271. This resulted in the virtually complete inhibition of metastases arising from human melanoma tumours in mice [7].

Cancer is GMO

What is the origin of cancer? It is an interesting question. If about 10% to 20% of cancers originate from exogenous viruses, then where does the other 80% to 90% of cancers originate?

We observe two phenomena:

1. Most cancers originate from fast replicating cells, such lung and colon cells.

2. The main trait of cancer is proliferation, similar to the unicellular organism's trait, and same as the virus's trait.

Normally, the GMO is a process of manually incorporating new genes into an organism to create one or more traits that are not already found in that organism. In cancer development, whether a gene was from exogenous viral genes or endogenous dormant genetic relics which are incorporated into the recipient cell by HGT, the GMO will express the traits of the genes from which it arose. The main trait is proliferation which is a typical unicellular organism trait.

If a virus invades the mammal cell, such as HPV, the virus resides inside the mammalian cell and relies on that cell to provide nutrients. If the DNA replication is faulty, such as a DSB, the repair may pick the genes near the point of the break and attach them to where it is broken. However, if the picked up genes are from exogenous viruses or endogenous viral genetic relics, then it has the virus's traits and the new GMO is a viral gene cancer (VGC). After the viral gene cancer develops, it flouts the normal cell's standard rules of growth. The other viral genetic relics could be incorporated into a new GMO by HGT. The new GMO will express all viral gene traits and its proliferation. The GMO could mutate to adapt to the microenvironment as well. This is one reason why cancer patient's cancer genomes are not the same.

Exogenous viral gene GMO

If the normal cell has viruses inside its cell and DNA breakage occurs, such as a cervical cell infected with the HPV virus, the new DNA may pick up the genes from the HPV virus and incorporate them into the new cell (HPV viral genes inserted into new DNA). This new cell is a GMO genetically engineered from HPV genes by HGT. The HPV vaccine would eliminate the effective HPV viruses, and hence reduce the possibility of HPV genetically engineering the new cells if the DNA replication is faulty, thereby reducing the possibility of cervical cancer.

Endogenous viral gene GMO

The viral genetic relics inside the cell are mostly dormant and provide limited function. If the viral genetic relics are incorporated into a new cell such as the GMO, the new cell will express the trait of the viral genes it arose from. Humans have about 8% retroviruses and other types of viral genetic relics in their genome.

Link between viruses and viral gene cancers

The new GMO will express the trait of viruses which is proliferation. With the following observations:

- In Booth's study, the combination of OSU-03012 (AR-12) and Viagra is an effective anti-cancer therapy [8]. The AR-12 is effective in treating a host of viral infections in the laboratory and in animal models, including HIV, Ebola, influenza and measles [9]

- In Salanti's study, the chondroitin sulfate (glycosaminoglycan) in the placenta was also present in cancer tumours [10,11]. Endogenous Retroviruses (ERV) actually play an essential role in placental development [12]. If the VGC was genetically engineered by retrovirus, then some VGC and placental cells will have the same traits because both were developed from ERV.

- In Katzourakis' study, the more the retroviruses in a given animal's genome, the higher chance that animal will develop cancer [13]

Viral Gene Cancer Treatment Strategy

Chemotherapy

The immune system may not be able to handle large tumour burden loads. Thus we need to reduce tumour burden to give the immune system a chance to eradicate the remaining tumour. This approach is similar to a severe bacterial infection requiring antibacterial treatment. The normal cancer therapies are surgery, radiation or chemotherapy. Unfortunately the maximum tolerated dosage of chemotherapy could damage the immune system which is desperately needed to eradicate the remaining tumours. It is a challenge to find alternative therapeutic options which would reduce tumour burden and not dampen the immune system. There are some possibilities to explore:

Immunotherapy

- EBC-46 is an extract from the blushwood berries of Queensland, Australia. A single intra-lesional injection of EBC-46 causes PKC-dependent hemorrhagic necrosis, rapid tumour cell death and ultimately the cure of solid tumours in pre-clinical models of cancer. A result from this therapy is the creation of an immune response [14,15].

- In Salanti's study, they created recombinant VAR2CSA (rVAR2) proteins to bond the chondroitin sulfate. Similar to the

Table 1: Comparison of ancient eukaryotic cell to late-stage cancer.

Traits	Ancient eukaryotes	Late-stage cancer
1. Hypoxia	yes (no oxygen existed)	yes
2. Anaerobic metabolism	yes (no oxygen existed)	yes
3. Glucose as an energy source	yes (glucose was product of photosynthesis)	yes
4. No cell adhesion trait	yes (ancient eukaryote lived in water)	yes
5. Cell stiffness reduced	yes (ancient eukaryote lived in water)	yes
6. Proliferation on soft tissues	yes (eukaryote lived in water, not on land)	yes
7. No cell contact limit	yes (eukaryote was unicellular organism)	yes
8. Mutation to adapt to microenvironment	yes (eukaryote was unicellular organism)	yes
9. Radiation & Chemotherapy Resistance	yes (no ozone protection & dormant capability)	yes
10. Innate immunity	strong	strong

malaria parasite, it is used to adhere to the placenta and add a toxin. This combination of malaria protein and toxin causes the cancer cells to die both in cell cultures and in mice with cancer [10].

- In Lizotte's study, the shells of a common plant virus, Cowpea Mosaic Virus (CPMV), inhaled into a lung tumour or injected into ovarian, colon or breast tumours, not only triggered the immune system in mice to wipe out the tumours, but the cowpea virus-based nanoparticles stimulates systemic anti-tumour immunity to treat metastazes [16,17].

- In He's study, they used the nanoparticles which assemble themselves from the chemotherapy agent oxaliplatin. A photosensitizing agent, pyrolipid, forms the outer layer. They injected the nanoparticles into one of the tumours. When light is shone on the pyrolipid, the synergy between oxaliplatin and pyrolipid-induced PDT kills tumour cells and provokes an immune response. It also activates T-cells that can recognise other distant cancer cells, like an anti-tumour vaccination [18,19]. Note that this is localised chemotherapy in contrast to systemic chemotherapy that could weaken the immune system.

- The Roberts' study used the Clostridium novyi (C. novyi-NT) bacterium by removing the bacteria's toxin-producing genes and directly injecting the C. novyi-NT spores. This produced a good anti-tumour response in rats and dogs. C. novyi-NT thrives only in oxygen-poor environments. The bacteria, once it has infected the tumour, can induce a strong immune response against tumour cells themselves. [20,21]

- In Krysko's study, the great power of immunogenic cell death is seen when the body's immune system becomes activated to specifically eliminate the cancer cells. Antigen-presenting cells phagocytize the necroptotic cancer cells and instruct the immune system to trace, recognise and kill any living tumour cells. Every second, one million cells die by a programmed cell death in a healthy human body. Immune cells efficiently clear the body of these dying cells without eliciting an inflammatory response. Elimination of cancer cells by the induction of cell death is also one of the main goals in anti-cancer therapy. This provides an alternative way to kill cancer cells by inducing another type of immunogenic cell death that is necroptosis, to kill cancer cells and to elicit a specific anti-cancer immune response. These results could pave the way for necroptosis as a novel target in cancer immunotherapy [22,23].

In necrotic cell death, cells undergoing necroptosis rupture and leak their contents into the intercellular space. I envisage that all the above therapies could kill some tumours. The dead cancer cell acts as an antigen and the immune system could create antibodies in response to it.

Ancient Eukaryotic Gene GMO

The mammalian genome was evolved from anaerobic eukaryotes rather than starting from afresh after the GOE. The ancient genes are deeply imbedded in the mammalian genome. The ancient genes are fewer in quantity in comparison with viral genetic relics in the genome. If the viral gene tumour developed further, as the cells have chaotic replication, then ancient genes with anaerobic metabolism could be incorporated into new GMO cells such as the Ancient Gene Cancer (AGC). The AGC would express the traits of an ancient eukaryotic organism (Table 1).

Notes:

1. Non free oxygen environment for ancient eukaryotic cells until all Earth's oxygen sinks are saturated. The ancient eukaryotes lived in a hypoxic environment, similar to the late stage cancer tumour microenvironment that is hypoxic.

2. The ancient eukaryotes lived in a hypoxic environment with anaerobic metabolism. Late-stage cancers choose anaerobic metabolism even in the presence of oxygen. The tumours proliferate aggressively in hypoxia in comparison to oxygenated environment [24].

3. Glucose was a by-product from photosynthesis in ancient times. Cancer's main metabolism source is glucose, but will use glutamine instead if glucose is scarce.

4. The ancient eukaryotic cells lived in water, hence its trait of showing no adhesive properties. The late-stage cancer cell's adhesiveness decreases as the cancer progresses. The consequence is that:

a. In the Hirohashi study, the cell adhesiveness is generally reduced in cancers, loss of cell-to-cell adhesion and inactivation of E-cadherin expression [25].

b. In Pal's study, loss of E-Cadherin as a prerequisite for metastasis in many cancers [26].

c. In Milano's study, the cancer cells often lack E-cadherin, a sticky protein, and can slide around the other cells if they bump into them [27]. The ancient gene cancer cell could break away from the tumour cluster because of the lack of adhesion and metastasize to other organs.

5. The ancient eukaryotes were unicellular organisms living in stormy waters. A softer cell would easily adjust the water pressure if the organism was not on the water's surface and would be subject to less impact stress if the cells hit any objects. A softer GMO could more easily metastasize by squeezing through the extracellular matrix. There are a few studies regarding the cell's stiffness:

- In the Jayo study, cancer cells have unusually high levels of fascin protein. The fascin protein enables cancer cells to deform and squish through the small intercellular matrix, with the nucleus reliably springing back to its original shape [28].

- In Fraldi's study, it was shown that the cancer cells are less stiff as the cancer progresses. Experiments performed on individual cancers and healthy cells of different types demonstrated that the former were about 70% softer than the latter, and the increase in cell deformability is directly related to cancer progression. The metastatic cells could pass through rigid capillaries whose diameters are smaller than tumour cells [29].

- By using ultrasonic waves, it was shown that the cancer cells are in different layers according their stiffness. The softer the cell, the worse the prognosis [30].

6. One trait of ancient eukaryotes was proliferation in water and it would be dormant if washed onto rocks. In Tan's in vitro study, the cancer cells only proliferated on soft tissues and are dormant on a stiff substructure. The protein Sox2 expression is necessary to sustain the self-renewal capability of Tumour-repopulation cells both in vitro and in vivo [31]. Cancer mostly metastasizes to soft tissues such as lung.

7. Normal cells would not replicate if in contact with other cells. The ancient eukaryote was a unicellular organism which did not care if other cells are in its way. Cancer cells just disregard this orderly environment.

8. Similar to ancient eukaryotes which lived in a rough environment, cancer cells mutate quickly to adapt to their microenvironment.

9. The ancient eukaryotes did not have an ozone layer to protect them from ultraviolet radiation from space if they had been washed onto rock. Therefore the best course of survival is to become dormant. Similarly I envisage the ancient gene cancer became dormant when it faced assaults. Ultimately, no cancer DNA damage occurs if the cells don't take input drugs while in dormancy. Any surviving cancer cell would repopulate the tumour after therapy is over [32]. In Keysar's study, they found that the PI3K pathway, which is the most common alteration in head and neck cancer, then deploys SOX2, a transcription factor, to activate programs that modulate 'stemness' within the cell's nucleus. For example, SOX2 was found to control aldehyde activity, which is a common cancer stem cell marker and a well-known driver of cancer stem-cell-mediated tumour growth. In normal cells, PI3K is used as a sensor for energy, but for a cancer cell to act cancerous, it needs metabolic flexibility -- it needs to be able to over-use energy -- and so this 'energy sensor' is a pathway it wants to hijack. After chemotherapy, PI3K helps the cell shut down and weather the storm. Then when the chemotherapy is gone, PI3K helps cancer stem cells start back up again. Chemotherapies kill rapidly-dividing cells. PI3K shuts down a cancer stem cell's metabolism, placing the cell in a dormant state. When the group eliminated SOX2 in mouse models of head and neck cancer, tumours became sensitive to therapies that previously had failed. But when the group amplified SOX2, tumours became even more resistant [33,34]. In Willers study, Cells irradiated in the absence of oxygen are 2- to 3-fold more radioresistant than well-oxygenated cells, also known as "oxygen effect" [35].

10. The ancient eukaryotes have the strongest innate immunity in order to survive in competition with other living organisms. Late stage cancer has this strong innate immunity, so they will prevail over the viral-gene cancers in cell competition.

In Lisanti's study, mitochondria are believed to have descended from bacteria which joined with cells early on in the evolution of life. This is why some of the antibiotics which are used to destroy bacteria also affect mitochondria, though not to an extent which is dangerous to humans. In lung cancer patients, azithromycin (an antibiotic used) increased one-year patient survival from 45% to 75%. Even lymphoma patients who were 'bacteria-free' benefited from a three-week course of doxycycline therapy, and showed complete remission of the disease. The antibiotics effectively treated certain metastasized tumours [36,37]. This shows that the ancient gene traits exist within late stage cancers.

Hallmarks of cancer

As the late-stage cancer cells have the traits of ancient genes, the "Cancer is a GMO hypothesis" could explain the hallmarks of cancer as follows:

Tumours have two states:

- The mammalian VGC will express the traits of viral genes from which it arose, it's aerobic metabolism organisms.

- The deeply imbedded ancient genes could genetically engineer into AGC, its anaerobic metabolism organisms, also known as Warburg effect.

Tumours are heterogeneous:

- After the viral gene GMO develops, it flouts the normal cell's standard rules of growth, and has chaotic DNA replication.

- It develops into two main groups, VGC and AGC, along with many subgroups. This is the reason why no two cancer patients have the same cancer genome.

Tumours can metastasize into other organs:

The AGC has the same traits of ancient eukaryotic cells which lived in water without adhesion and less stiffness:

- The AGC could break off from tumours because of the lack of adhesiveness.

- AGC could squeeze through the extracellular matrix, and enter and leave the blood vessels, because of less stiffness.

Resist chemotherapy by being dormant:

The AGC would respond to external assaults, such as the efflux pumps to pump the toxins out. The ultimate defence is dormancy as no chemical could enter the cell if it is in a dormant state [32].

Resist radiation by hypoxia and dormancy:

The AGC would resist most radiation under hypoxic environment. The ultimate defence is dormancy as there is no substantial DNA damage if it is in a dormant state.

Tumour proliferation:

The virus and ancient eukaryote are unicellular organisms and have the natural trait of proliferation.

Proliferation on soft tissues:

The ancient eukaryotes lived in water, proliferated in water and are dormant if washed onto land.

The AGC has the same trait as the ancient eukaryote and metastasizes into soft tissues.

Currently there is only circumstantial evidence and not robust scientific proof. However, if we compare it to evolution, it gives us confidence that the assumption is reasonable.

Ancient Gene Cancer Therapy

The ancient eukaryotic cells that lived in water more than a billion years have the strongest innate immunity and survival ability. The AGC is a difficult cancer to eradicate. There are common traits among the GMO, such as:

- Glucose as metabolism source
- Lactic acid generated by fermentation
- Hypoxic environment
- Poor adaptive immunity
- No cell adhesion
- Less cell stiffness, with softer membrane

One of the proposed therapeutic strategies is to use oncolytic viruses to kill some of the cancers, which would create antigens from the dead body of cancer cells. The immune system would create an antibody in response to the antigen. The antibody could eradicate other distant tumours as well. The challenge is that oncolytic viruses would not stay very long in the circulation system and would be eradicated by the immune system eventually. I suggest the use of nanoparticles to weaken the AGC which will give the genetic engineered viruses a chance to quickly kill some of the cancer cells prior to it being eradicated by the immune system.

Weakening cancer by nanoparticles

- I envisage that a nanoparticle's mechanical vibration could be an effective weakening therapy. It would involve a magnetic nanoparticle coated by glucose under a low alternative frequency magnetic field, based on the following assumptions:

- Aerobic metabolism is 19 times more efficient than anaerobic metabolism. The ancient gene GMO requires 19 times more glucose than normal cells to produce the same quantity of ATP. The glucose coated nanoparticle would function as a trojan horse to enter the GMO, and the glucose coated nanoparticles may not be rejected by immune system.

- The amount of nanopaticles to enter a cancer cell compared to the normal cell would be more than the ratio of 19 to 1, if the external low frequency alternative magnetic field strength is limited in order to not hurt the normal cells. But it will have 19 times more impact on the AGC.

- We could add a middle layer of anti-cancer chemicals in between the magnetic nanoparticle and glucose if necessary. After nanoparticles enter the cancer cells, the mechanical vibration could strip off the outer glucose layer and expose the cancer cell to the anti-cancer chemical [38].

- Alternatively, a high frequency magnetic field could generate heat to weaken the cancer cells. Again, the magnetic field strength should be kept low in order to not hurt the normal cells. I envisage, however, that the mechanical vibration will be more effective than heating because the ancient eukaryotic organism has had more exposure to high temperatures when the organism was washed up onto rocks. Hence the tumour may be more tolerant to heat than normal cells.

- In Hao's study, certain colorectal cancer cells reprogram their metabolism using glutamine, a non-essential amino acid. Many cancer cells rely on glutamine to survive [39]. Instead of glucose coated nanoparticles, we could use glutamine coated nanoparticles to treat glutamine dependent tumours.

Proposed combination of weakening AGC and antigens creation

1. Use nanoparticles to weaken the AGC.

2. Use one of the antigen creation strategies to kill some tumours, the cancer's dead proteins are broken down into smaller peptide fragments as antigens.

3. The immune system may eradicate the distant tumours in response to the antigens.

4. This strategy could offer multiple therapies as the cancer cells have less chance to develop resistance.

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