

[OPINION] Cancer – A Case of Good Design Turned Awry

In the beginning... darkness covered the surface of the Earth that was filled with an aura of mystery and shrouded with a thick heavy mist of water. When life was found on Earth some 3.6 billion years ago after the thick mist coalesced, the earliest life form was a marine dwelling of single-cell organisms.

Fast forward 3.0 billion years, creatures developed bilateral symmetry that bore a resemblance to fish. During the Cambrian explosion, fish became the first known vertebrates and the genesis of all tetrapods (land-walking vertebrates).

Fish then developed jaws during the Devonian period as part of morphology driven by survival. Jawed fish further evolved with time into two surviving groups – the cartilaginous fish and the bony fish.

The cartilaginous fish remain in oceans to be the sharks of today and the bony fish further evolved into ray-fin and lobed-fin fish. Ray-fin fish are the myriads of fish species inhabiting both fresh and salt waters today.

The lobed-fin fish, compelled by ecological and competitive pressures, sought existence on land. Powered by fleshy fins and internal bone structure, they adapted to the demands of land habitation without losing their aquatic abilities to become amphibians.

Of course, evolution did not stop here– for the amphibians progressively developed into land-dedicated reptiles, reptiles into mammals, and mammals into man.



The coelacanth, a prehistoric lobed-fin fish from the Devonian Period and the only living fossil in the world

From amoeba to humans, we have just painted a picture of the evolution of man over 530 million years in a single paragraph.

To the modern-day oncologist, however, this pretty visual of human evolution is the work of gene mutation, the very cause of many a dreadful disease, including cancer.

Evolution is the necessity of survival and existence. Morphology is therefore justified by functionality. That's why pigs have trotters and we have fingers and toes. I say that again. Fingers and toes and not fingers or toes. And pigs were mentioned here not without a reason.

As a continuing process, the essence of these traits is captured over time and coded in the genes stored in living cells. Genes are linear sequences of molecules chemically bonded together, the full complement of which is referred to as a genome.

The human genome has some 20,000 genes that comprise nuclear DNA in 23 pairs of chromosomes and mitochondrial DNA. Genes are basic physical and functional units of heredity and are DNA segments that instruct cells on how to make proteins. Humans are 99.9% genetically similar to one another and share 98% of their DNA with pigs.

Under normal circumstances, the DNA is deemed to be stable and aligned with the demands of the external environment. Evolution through natural selection is the successful adaptation by creatures exposed to harsh environmental changes.

Evolution at a cellular level represents a gradual accumulation of cell mutations driven by altered DNA, especially in the germinal cell line. Most of these cell mutations are beneficial, reflecting appropriate and imperative survival adaptations that can be passed down the generations, though occasionally mutations can turn bad.

In 2015, a malignant tumour was found in the femur of a 240-million-year-old turtle-like reptile, the Pappochelys Rosina, demonstrating that cancer has been plaguing creatures since the Triassic Period. The osteosarcoma on the fossil might be one of the earliest known cases of cancer ever found.



Photo Credit: Brian Engh

240 million years of cancer from the extinct Pappochelys Rosina, a reptile known to be the “grandfather of turtles”.

From the foregoing, one can appreciate that not any cell mutation will lead to cancer. As a rule of thumb, it requires multiple mutations, usually double-digit occurrences, before a cell turns

possibly cancerous, and even in the case of inherited genetic abnormality, the defect counts toward one mutation that predisposes the individual towards malignancy.

Suffice it to say, time is a precondition for multiple mutations to occur which is why cancer is a disease of old age. Aside from sporadic exogenous assaults that damage cellular DNA, the very act of biological self-renewal may cause progressive DNA abnormalities if the accuracy of DNA replication during cell division is compromised.

The human body replaces 330 billion cells daily and cell division is akin to a situation where copies of an original document are generated from the same photocopier. What can one say about the sharpness and resolution of images after a million reproductions as compared to that of the original document? Given the high cell turnover rate, random transcription or replicative errors leading to altered DNA are inevitable.

According to the National Cancer Institute, the average age of individuals first diagnosed with cancer in 2020 is 66, which means about half of the cases are diagnosed in people 66 and older, with risk increasing with age. It is a foregone conclusion that cancer shall come to a calling when one lives long enough.

To further complicate matters, not all cell mutations are equal.

There are two major categories of mutations – somatic and germline mutations. Germline refers to reproductive cells and all other cells are deemed somatic. DNA alteration or damage that is not duly repaired in non-replicating cells will result only in accelerated cell ageing.

Only the same thing happening to replicating cells or stem cells will lead to cell mutation. Germline mutations occur in gametes and can potentially be transmitted to offspring, with every cell in the offspring being mutated.

We earlier mentioned genes, genomes, and DNA, with genes being specific functional units of genetic material embedded in the DNA. Given that only 2% of DNA is coding for genes, it is arguable that the probability of any DNA alteration that could cause a loss of functionality is relatively remote with most sporadic mutations being harmless.

In cancer, mutations in any oncogene, a tumour-suppressor gene, or a gene that controls the cell cycle activity that generates a clonal cell population with a distinct advantage in proliferation qualify for count towards multiple mutations.

Cells are also not completely defenceless to attempts to change their constituent DNA. There is a defence mechanism within the cell structure to reduce the deleterious impact of possible cell mutation.

This is a system of tumour suppression genes and immunological functions that repairs and arrests DNA damage and in the event of irreparable damage, terminates the cell's existence via apoptosis or programmed cell death.

The TP53 gene provides instructions for making a protein called tumour protein p53 (aka guardian of the genome). Acting as a tumour suppressor, it regulates cell division by keeping cells from growing too fast and proliferating in an uncontrolled manner.

There is yet another inbuilt defence designed to protect and preserve our DNA genetics from replicative errors during cell division.

Telomeres, at both ends of each chromosome, maintain chromosomal stability, prevent chromosomal degradation and interchromosomal fusions. Another telomere function limits cell replication that indirectly puts a brake on malignant cell proliferation.

Summarising the discussion so far, three broad classes of triggers can categorically cause cell mutation with cancer-related genetic changes – hereditary, environmental, and replicative errors.

A 2017 study made of 32 types of cancers observed that 66% of cancer-promoting mutations arose randomly during cell division in various organs throughout life, with 29% mutations traced to environmental insults, and 5% being inherited.

Although the big data demonstrated that the enemy appeared to be from within and had a less than predictable occurrence, the study also qualified that cancer types did show logical deviations from the findings like pancreatic cancers are caused primarily by replicative errors as opposed to environmental causes for lung cancer.

Cancer, an ancient disease since prehistoric times, is today an ailment of old age whose vice-like grip is increasingly reaching out to the younger generation.

Driven by the same enigmatic force of genetic change and cellular mutation that propelled evolution forward since time immemorial. Under restraint, it allowed life forms to surmount adversities and brought us to where we are today after 530 million years. In rage, it causes cancer within the lifespan of man.

One last illustration to bring home the point – a story about fingers and toes.

Not again?

Early during gestation, and perhaps as a reminder that man evolved from fish, the fingers and toes of a developing human embryo are webbed together like fins. However, before the eighth week of pregnancy, the connecting tissue starts to dissolve, and individual fingers and toes

emerge elegantly by sheer operation of apoptosis through a protein Sonic Hedgehog (not the Japanese video game character).

Babies born with fused fingers and toes suffer from a genetic defect called Syndactyly. A loss of apoptosis resulting in cell immortality is one of the principal causes of cancer.

Life holds many mysteries that are fascinating, yet complex and technical, that can be engaging in discussion for many people.

Cancer is just one of them.

This article has barely scratched the surface of the topic. Going forward in the journey of discovery, it would doubtlessly be more arduous and demanding as we delve deeper into the world of cancer.

Perhaps not for the reader but the storyteller who shall, in the words of Einstein, “make it as simple as possible but no simpler”.

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