Communication

Evolutionary, Non-Mutational Cancers Cannot Be Considered Atavistic

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Posted Date: 30 September 2023

doi: 10.20944/preprints202309.2156.v1

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Evolutionary, Non-Mutational Cancers Cannot Be Considered Atavistic

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Abstract: Recent successes in the field of evolutionary cancer cell biology (ECCB) have brought to a head two of the most important controversies regarding cancer origin. The first concerns the question of whether carcinogenesis is initiated only by genetic alterations, mutations, and driver genes, as the mutational theory teaches. The ECCB, claims that a large number of polyploidy-related cancers (PGCC cancers) are not due to mutations, but rather to inadequate ancient repair mechanisms used by DNA-damaged stem cells for their repair. Somatic mutations are merely secondary. The second controversy, described in the previous article, concerns the non-mutational theory itself: Are non-mutational polyploid cancers an atavism - as previously thought - or rather the effect of an ancient gene regulatory network aGRN that controls genome reprogramming in precancerous DNA-damaged cells as well in the transformed cells. Finally, the unicellular gene module of cancer, of which the aGRN is a part, has evolved along with the multicellular genome during the last 1000 My of evolution. and non-mutated cancer cell systems are under the control of the aGRN. The atavistic theory relies on phylostratigraphic evidence to determine the age of cancer genes**.** It states that most cancer-like genes arose during the transition period from unicellularity to multicellularity, but also during the early metazoan era. In our opinion, the atavistic theory is flawed and suffers from many misunderstandings. It provides little insight into the origin and coevolution of the cancer cell system and its control by the ancient gene regulatory network aGRN.

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In contrast to the atavistic hypothesis, Evolutionary Cancer Cell Biology [1–4] focuses on three processes that are crucial for cancer development: (i) the breakdown of the ACD phenotype with the loss of function, such as stemness, differentiation, and cell plasticity potential, (ii) the conversion of the damaged ACD phenotype into a defective symmetric cycling phenotype (DSCD phenotype) that needs to be repaired, and (iii) the adoption of a unicellular repair mechanism that reprograms the genome of the defective multicellular DSCD into a precancerous cell state with unicellular imprinting. In humans, there is a large precancerous DSCD cell family with VSEL cells, RR cells, and extragonadal GSCs [1,2,5].

DNA-damaged stem cells needing repair as a pre-cancerous cell state

In a most popular statement issued in 2023, Khan Academy gives the current scientific opinion on the fate of DNA-damaged cells and stem cells. It states that cells normally recognize the damage and try to repair it. If the damage cannot be repaired, the cell sends itself into apoptosis. If the defective cells do not undergo apoptosis, they are thought to be precancerous and on their way to becoming cancerous [6].

It is becoming increasingly clear that the transformation of "unhealthy" stem cells into CSCs may occur not only by mutations but also by environmental changes in tissue and stem cell niches and reprogramming. Non-mutational reprogramming is common in carcinogenesis and tumorigenesis. At least 90% of undifferentiated colorectal and glioblastoma carcinomas [7] have PGCCs as genome repair structures. They are responsible for the oncogenic transformation and generation of CSCs [2].

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As the microenvironment has a critical role in regulating stem cell function, alterations to the niche play a pivotal role in the development of cancer. Because the balance between stemness and differentiation depends on conditions in the niche, niche alterations at the signaling or structural level could lead to the development of cancer [8–10].

Oncogenic transformation through inadequate repair and reprogramming

DSCD cells survive DNA damage. They await repair, genome reconstruction, and function regain, i.e., stem cell restoration, non-gametogenic germline (NG germline) restoration, and resumption of stem cell generation. DSCDs are capable of transient proliferation through a defective symmetric cell cycle, but can enter a state of transient quiescence or slow cycling in niches. When environmental changes or leaving the niche and exposure to more oxygenated regions increase proliferation, DSCD progeny become fusible and form cell aggregates. This is preliminary evidence that under the influence of environmental changes, the DSCD progeny is ready to start a repair process of unicellular imprinting, which is unusual for multicellular cells.

In the absence of a suitable multicellular repair mechanism, the DSCD progeny reactivates an ancient PGCC-like mechanism driven by the genes of the conserved aGRN. Thus, repair and genome reconstruction proceed in the unicellular direction, changing the precancerous DSCD phenotype into an oncogenic ACD phenotype, with stemness and differentiation potential and the ability to initiate the evolutionarily lower germ and soma (G+S) life cycle of cancer. It contains all the features of the Urgermline developed by the AMF ancestor and produces germline stem cells (naive CSCs).

Ancestral roots of cancer and evolution of the cancer genome

Evolutionary cancer cell biology uses current knowledge about the deep homology between the life cycles of cancer and protists that live in a similar oxygen gradient as cancer cells [1–5]. It paints a much more detailed picture of the ancestral roots of cancer, including the external influences that transform normal cells into irreversibly damaged cells, and how and why these damaged cells progress to oncogenesis. It shows that the oldest roots of carcinogenesis lie long before the transition period to multicellularity, namely in the time of the first oxygen explosion about 2.3 Gya ago. Genes used by the ancestral life cycle of cancer are founded by the common AMF ancestor, which branched into the clades of amoebozoa, metazoa, and fungi.

Certain genes of this ancient network and their derivatives regulate and control other important non-cancerous functions in humans and metazoans. AMF genes regulate embryonic processes, ESCs, non-gametogenic (NG) germlines, as well as stemness, differentiation, symmetric and asymmetric cell division (ACD and SCD), and cell plasticity (soma-to-germ transition). The genes of the AMF genome were evolutionarily adapted to the actual needs of metazoans and not removed from the metazoan genome.

The susceptibility of the ACD cell phenotype to more oxygen than 6.0% O2 is inherited from the AMF ancestor and shows the non-gametogenic Urgermline sensitivity to hyperoxia at the time. This susceptibility to oxygen is inherited by all NG germline metazoans, including humans, and cannot be successfully repaired. It leads to DNA damage and the DSCD phenotype as a cancer precursor cell.

The non-mutational mechanisms generating PGCC cancers are ancient evolutionary mechanisms developed by the common AMF ancestor of amoebozoans, metazoans, and fungi. They evolved during the evolution of pre-metazoans and metazoans and also during the evolution of carcinogenesis. Oncogenic transformation is an evolutionary process of premetazoan imprinting that has continued in early metazoan cancers but also parallels the evolution from lower to higher metazoans and humans. The carcinogenesis itself is not a simple atavism or a simple process of reverse evolution. It has evolved during the life history of metazoans against the multicellular system and in the struggle with multicellular genes (MG), which were gradually abolished by unicellular genes (UG) [11–13]. This is not an atavism, but a process of progressive co-evolution to metazoans.

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Weaknesses and errors of atavistic theory

The atavistic theory [14–16] relies on phylostratigraphic evidence to determine the age of cancer-like genes [11–13]. It claims that the most genes expressed in cancer arose about 1000 Mya ago during the long period of transition from unicellularity to multicellularity, but also after that in the early metazoan era. In our opinion, the atavistic theory is flawed and suffers from many misunderstandings. It does not provide information about the life cycle of cancer and the control of the cancer cell system by the ancient gene regulatory network aGRN

Chronologically, the atavistic theory underwent three successive developmental phases: The first phase occurred between 2007 and 2010 and was initiated by the phylostratigraphic studies conducted by Domazet-Lošo et al. [17]. The second phase encompassed the years 2017 to 2019 and involved molecular biological studies conducted by Trigos et al. [11–13], and the third phase spanned from 2019 to 2021, during which time the atavism hypothesis was formulated in its final form by Bussey, Davies, and Lineweaver.[14,15].

As reviewed by Thomas et al [18], the parents of the atavistic theory understand cancer as a kind of return to earlier evolutionary capabilities. This ancient program evolved, according to the authors, in the pre-metazoan era, a time when unicellular organisms were subjected to pressures that promoted the proliferation of cellular life under difficult and often adverse environmental conditions. These adaptations did not necessarily erase the ancient genetic programs, but suppressed their activation, at least for the duration of an organism's life.

In our opinion, not only the use of the term atavism but also several statements of the atavistic theory are problematic, and argue even against it. The parents of the atavistic idea consider that cancer is a sequence of atavistic reversals to the "*serial development which would inversely correlate with the time sequence in which the relevant cancer genes develop*" [14–16].

First, the atavistic model predicts that the lost traits are younger multicellular traits, while the gained cancer abilities are older traits. But that would mean what the atavism theory does not want to claim at all, namely that the AMF genes became better and better protected in the course of evolution (even better protected than the younger multicellular genes (MGs) and express more and more functions. In other words: more and more selective evolution of unicellular genes (UGs) and less and less atavism.

Second, the parents of the atavistic idea claim that phylostratigraphic studies have identified *mutation patterns* that represent a return to genes that evolved with the transition to multicellularity. The ECCB does not support this assumption and shows that the oncogenic process is largely non-mutational and that cancer exploits an ancestral gene module, that evolved long before the transition period but was enriched in the transition period by a variety of additional dead-end genes [1,2] that may be used in later carcinogenesis and tumorigenesis.

Third, the idea of a *general dysregulated and uncontrolled mitosis* as the core of cancer cell proliferation, arising from the progressive loss of cell cycle checkpoints, does not account for the oxygen-sensitive NG cancer germline, which produces cancer stem cells (CSCs). Unfortunately, the atavistic theory does not distinguish between (i) the unaffected productive cell cycles that the ACD phenotype undergoes and the normal mitoses controlled by the ancestral regulatory aGRN, (ii) the defective symmetric cell division (DSCD) of the oxygenic-stressed NG cancer germline that loses stemness and differentiation potential [2,3,5] and (iii) the unlimited cell divisions of the somatic SCD phenotypes. Finally, we consider that a disease that regularly affect 50% of each generation of humanity cannot be considered atavisms.

Conclusions

According to Evolutionary Cancer Cell Biology, DSCD cells are collapsed ACD phenotypes with DNA damage that lose stemness and await repair. They occur in all NG germlines, stem cell lines, and ACD cell systems (Urgermline offsprings) such as embryonic, adult, or germ stem cells. in all these cell systems DNA DSB induced by stress or excess oxygen cannot be repaired by the modern DDR mechanisms of humans and metazoans. However multicellular organisms have not evolved

appropriate mechanisms to repair their ACD and DSCD genomes; they still rely on the ancestral MGRS repair mechanisms, with cell and nuclear fusion and hyperpolyploid giant nuclei.

The question is why this is so. As we can see, the gene package inherited from the AMF ancestor is complex and provides for gene regulation in stemness and differentiation. AMF genes for stemness and differentiation coevolved with the multicellular genome and survived millions of years. Oddly enough, the ACD phenotype in humans and metazoans is still oxygen-sensitive, can transform into the DSCD phenotype, and can survive dormant phases. They are not directed into apoptosis and await genome repair. However, multicellular organisms have not evolved appropriate repair mechanisms and use ancient AMF mechanisms that are older than 2.0 Gy and unable to repair the multicellular DSCDs of humans. Cancer is not a disease in the sense of the atavistic theory, but a disease caused by inadequate genome repair mechanisms.

We disagree with terms such as "atavistic regression," "networks of atavistic attractors," or "epigenetic nature of oncogenic transformation," all of which lead to confusion. In our opinion, non-mutational carcinogenesis is a process of inappropriate and therefore failed repair to the DNA-damaged cells of the multicellular organismsus. It originates from the common AMF ancestor, was developed for the repair of unicellular germline cells, and is the only repair system of its kind that is also available to defective multicellular stem cells to regain stemness and differentiation potential from DNA damage and loss of function at unicellular this by the only available repair pathway capable of restoring stem cells and ACD potential. Since this mechanism proceeds via polyploid MGRS (PGCC-like) repair structures subordinate to the ancient gene regulatory network aGRN, the multicellular DSCD genome is reprogrammed according to the rules of the unicellular rather than according to the multicellular cell system. The reprogrammed cells acquire stemness and differentiation potential but follow the ancestral germ and soma G+S life cycle. Under the control of aGRN, normal non-cancerous stem cells do not develop, but CSCs and cancer. Nevertheless, cancer is not an atavism but a case of symbiotic coevolution, environmental adaptation, and selection.

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