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Cancer progression as a sequence of atavistic reversions

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Abstract

It has long been recognized that cancer onset and progression represent a type of reversion to an ancestral quasi-unicellular phenotype. This general concept has been refined into the atavistic model of cancer that attempts to provide a quantitative analysis and testable predictions based on genomic data. Over the past decade, support for the multicellular-to-unicellular reversion predicted by the atavism model has come from phylostratigraphy. Here, we propose that cancer onset and progression involve more than a one-off multicellular-to-unicellular reversion, and are better described as a series of reversionary transitions. We make new predictions based on the chronology of the unicellular-eukaryote-to-multicellular-eukaryote transition. We also make new predictions based on three other evolutionary transitions that occurred in our lineage: eukaryogenesis, oxidative phosphorylation and the transition to adaptive immunity. We propose several modifications to current phylostratigraphy to improve age resolution to test these predictions.

Keywords

Atavistic model; cancer; eukaryogenesis; evolution; phylostratigraphy; somatic mutation theory

INTRODUCTION

Following the sequencing of the human and other genomes, phylostratigraphy has been used to determine the evolutionary ages of genes shared across species.[1] Applied to cancer genes, phylostratigraphy has confirmed the longstanding view that cancer represents a type

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CONFLICT OF INTEREST

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of throwback or atavism, a claim originally suggested in 1914 by Boveri.[2] We developed this general idea and couched the atavistic model within the dichotomy Metazoa 1.0 and Metazoa 2.0.[3,4] We compared tumorigenesis to a flip-to-safe mode, unlocking the ancient toolkit of Metazoa 1.0. This suggested that the atavistic model was about a one-off atavism, similar to well-known morphological atavisms that appear during development.[5-8] As a result, the atavistic model of cancer has often been understood as a single, one-off atavistic reversion from a multicellular to a unicellular mode of life. This dichotomy is easy to grasp and got the basic idea across, but is too simple to match the complicated reality of cancer onset and progression. Here, we argue that the relationship between cancer progression and atavistic reversions is more continuous. We argue that cancer is not a single atavism, but a series of atavisms. To more accurately reflect this, we introduce an improved version of the atavistic model that includes a sequence of atavistic reversions, not just a multicellular-to-unicellular switch. We call it the Serial Atavism Model (SAM). The novelty of this new model is its reliance not just on one, but on several deep evolutionary transitions.

The principal hypothesis is that as neoplasms evolve in the host, the sequence in which cancer hallmarks become manifest is not random, but roughly correlates inversely with the chronological sequence in which the relevant genes evolved. Advances in phylostratigraphy now enable this idea to be tested.

It is generally recognized that the genes responsible for cellular cooperation in multicellular organisms (e.g., signaling, adhesion, angiogenesis, migration) are precisely those genes that are corrupted in cancer and lead to loss of regulatory function.[9-12] Consistent with that observation, several research groups[13-20] making use of phylostratigraphy have identified reversionary patterns of expression and mutation among genes implicated in cancer, corresponding to the unicellular-to-multicellular transition which occurred roughly a billion years ago (Figure 1).

Unlike familiar morphological atavisms, such as supernumerary nipples which involve a one-off ontogenic transition,[5-8] cancer is a multi-stage process in the direction of increasing malignancy. Correspondingly, a description of cancer as a simple reversion from multicellular to unicellular form is too simplistic. It is therefore more accurate to view cancer as a sequence of reversionary transitions. We call this the Serial Atavism Model (SAM). A key prediction of SAM is that the reversionary sequence should display regularities across species and across cancer types.

Cancer is conveniently characterized as displaying a set of distinctive common hallmarks, [26] some of which represent gain of function and some loss of function. Significantly, cancer does not evolve the hallmark properties ab initio; rather, neoplastic phenotypes are preexisting modalities latent in the genome,[15,25,27] retained because they play critical roles in key processes such as embryogenesis, tissue maintenance and wound healing.[9,28] Hanahan & Weinberg[26] remark: “The order in which these hallmark capabilities are acquired…appears to vary across the spectrum of human cancers.” However, according to our new model there should be identifiable patterns in the direction, order and timing of both the loss and gain of function as cancer progresses, occurring via a sequence of increasingly malignant transformations with no fixed termination except for the death of the

patient.[29] Evidence for the non-random nature of hallmark acquisition is shown in Table 1. Column 1 lists the types of physiological or cellular systems affected in cancer. Column 2 lists the normal abilities within those physiological systems that are lost as the hallmark abilities in column 3 are acquired by cancer cells. The juxtaposition of columns 2 and 3 exposes a systematic directionality in cancer progression. The atavistic model predicts that the lost abilities (column 2) evolved more recently, while the abilities gained (column 3) are more ancient. Column 4 identifies the normal (but often latent) roles of the abilities gained. Column 5 contains phylogenetic molecular-clock-based dates for the approximate origin of these abilities, inferred from our common ancestors who share these abilities (Figure 1). The dates are approximate and subject to some ambiguity; for example, should one use the date of the origin of a gene, or of its co-option for a new function?[30,31]

Four billion years of evolution have produced many evolutionary transitions that have left traces in cellular physiology and the age distribution of human genes. The Last Universal Common Ancestor (LUCA) of all extant life on Earth lived about 4 billion years ago (Figure 1). From ~4 billion years ago to ~1 billion years ago our lineage was unicellular (Figure 1, nodes 46-32). The appearance of multicellularity is represented by node 32, when our lineage diverged from the lineage that led to choanoflagellates. The emergence of multicellularity was an extended process beginning about 1.5 billion years ago with loosely-knit eukaryotic assemblages that eventually evolved into more tightly-knit colonies.[43,44]

There are many extant colonial organisms whose ancestors diverged from our lineage between nodes 37 and 32. From about 1 billion years until 0.5 billion years ago the colonies became more integrated, leading to organisms with a variety of specialized cell and tissue types that characterize most extant multicellular life forms.[45,46]

In seeking to ground cancer characteristics in evolutionary chronology, it is fruitful to also examine developmental chronology. The link between the two was identified as long ago as 1828, when von Baer[47] proposed a '4th law of embryology': "The embryo of a higher animal form never resembles the adult of another animal form, such as one less evolved, but only its embryo." This general trend was famously captured in Haeckel's aphorism "ontogeny recapitulates phylogeny."[48] However, the phrase is misleading and has been much criticized.[49-51] While it is certainly not a rigid law, it can nevertheless be a useful guiding framework,[52] and receives support from the so-called hour-glass model of embryogenesis.[53] For a dissenting opinion see,[54,55] according to which complex interactions between genes, cells and developmental processes peak during mid-embryogenesis when the basic body plan of the organism is being established. Kalinka and collaborators[56,57] found evidence for this phylotypic stage during mid-embryogenesis in which patterns of gene expression were highly conserved across animal species compared to earlier and later stages. See also.[14,58-60]

PREDICTIONS ASSOCIATED WITH THE UNICELLULAR-TO-MULTICELLULAR TRANSITION

As already remarked, phylostratigraphy confirms the general idea that cancer involves an atavistic reversion from a multicellular to a unicellular phenotype.[13-20,25] The evolution of vertebrate multicellularity was a multi-stage process that took about a billion years (~1.5 to ~0.5 Gya). Thus, the ages of the genes responsible for the beginning of this transition are separated by about a billion years from the genes responsible for the end.

A novel aspect of SAM is the hypothesis that multi-stage cancer progression reverses this multi-stage evolutionary chronology. For example, during phylogeny, if there was a transition 1 followed by a transition 2, we predict that cancer progression will be characterized first by a reversion corresponding to transition 2, then a reversion corresponding to transition 1. This claim could soon be tested by a higher time-resolution phylostratigraphy.

Reversion to unregulated proliferation

The best-known hallmark of cancer is uncontrolled proliferation, which was a key characteristic of our unicellular ancestors. For the greater part of terrestrial history, life was unicellular. Our prokaryotic ancestors proliferated asexually through binary fission from ~4 Gya to about ~2 Gya. Mitosis evolved about 2 billion years ago in unicellular eukaryotes, but the gene networks regulating it evolved later, during the unicellular-to-multicellular transition.

The dysregulation of mitosis is at the heart of the unregulated cell proliferation of cancer,[9,61] which arises from the progressive loss of checkpoints in the cell cycle. Vleugel et al.[62] have used phylogenetics to identify the evolution of the spindle assembly checkpoint. Although most of the components of this checkpoint are ancient and found in all eukaryotes, the proteins Spindly and Zwilch are found in Ophistokonta (node 35, ~1.1 Gya) but not in our more distant cousins. Based on SAM, we predict that as cancer progresses, the proper functioning of Spindly and Zwilch will tend to be compromised before the older proteins of this checkpoint. SAM makes analogous new predictions for the most recently evolved components of other checkpoints.

Cancer stem-cell hypothesis and cell differentiation cascades

It is generally accepted that as cancer progresses, normal, well-regulated, cell differentiation cascades become truncated (“maturation blocks”). Fully differentiated cells can also de-differentiate and become more stem-cell-like.[37,63] As a result, neoplasms contain an anomalous proportion of immature cells.[12,15,64] This observation forms the basis of the cancer stem cell (CSC) hypothesis,[15,20,65,66] which led to the discovery of genetic signatures shared by cancer and embryonic stem cells.[67-69] SAM predicts that although cancer cells become stem-like in their proliferative abilities, unlike normal stem cells they are unable to produce fully functional differentiation cascades (Figures 2 and 3). In other words, cancer stem-like cells cannot produce the more recently evolved terminal products of the differentiation process. In this way, cancer cells resemble early ancestral stem cells

that predated our modern differentiation cascades. A profusion of immature cells is unable to perform the normal functions of fully mature cells. Chronic myeloid leukemia (CML) is an example; the chronic phase becomes the accelerated phase, which then becomes the blast crisis. As CML progresses, the hematopoietic differentiation cascade becomes increasingly truncated, producing increasingly immature stem-like cells.[74] Another example is the pre-cancerous maturation block of the differentiation cascade in the gastrointestinal tract. Stem cells at the bottom of the crypt in intestinal lumen begin to differentiate and migrate upwards, but do not differentiate fully and produce adenomatous polyps.[9]

The evolution of differentiation cascades took hundreds of millions of years and required the emergence of gene regulatory networks involving hundreds of genes and new epigenetic patterns. During the billion-year evolution of multicellularity (~1.5–0.5 Gya, Figure 1), the number of distinct cell types slowly increased to the several hundred we have in our bodies.[75] Thus, the differentiation cascades seen during human ontogeny are the product of a long evolutionary pathway in which different genes evolved to regulate their increasing complexity. SAM predicts that cancer's transition to "stemness" will not occur as an abrupt single transition but via a systematic sequence in which genes that regulate the later stages in the differentiation cascades will be the first to be corrupted, causing maturation blocks. These more detailed predictions of SAM conform to a nuanced version of the CSC hypothesis—a gradual reversion, as suggested by the middle panel of Figure 3. These predictions should soon be testable with the higher time resolution of phylostratigraphic analyses applied to the gene networks controlling differentiation cascades.

Why reverse order?

SAM hypothesizes that the order in which genes evolved is reflected (in reverse) during cancer progression (Figure 2); features that have evolved more recently are damaged first.[18] Why is this? Why wouldn't carcinogens produce random damage independent of gene age? Why doesn't the genetic instability (so often invoked as a cancer enabler) corrupt all genes equally? Why should the genes associated with the early stages of ontogeny and phylogeny be less susceptible to corruption?

The atavistic explanation is that more recently evolved functions (Table 1, column 2) are less critical for cell survival, and are thus less-well-protected and less-well-conserved. In that sense they are more vulnerable to corruption. By contrast, functions gained (Table 1, column 3) are evolutionarily older. These functions are more important for cell survival, and so are correspondingly better protected and conserved. Consequently, alterations that produce loss of function in younger genes are more common than alterations of the older, critical, functions.[76] If all genes were affected equally there would be no predictable order to cancer progression.

PREDICTIONS NOT ASSOCIATED WITH THE UNICELLULAR-EUKARYOTE-TO-MULTICELLULAR EUKARYOTE TRANSITION

The unicellular-eukaryote-to-multicellular eukaryote (UEME) transition occurred roughly in the time frame 1.5 to 0.5 billion years ago (Figure 1). Here, we discuss important

transitions which for the most part occurred outside of this time frame. Eukaryogenesis and the evolution of anaerobic glycolysis (the reversion to which in the presence of oxygen is known as the Warburg Effect) evolved before the UEME transition. The transition to adaptive immunity in vertebrates evolved after the UEME transition.

Eukaryogenesis: the origin of eukaryotic cells

Chromothripsis, aneuploidy and other forms of genetic instability are familiar hallmarks of cancer and have distinctive antecedents in our evolutionary history. Diploidy was established in the node interval 41-31 (~2 to ~1 Gya). Genetic instability has been recognized as an adaptive feature used to produce variation in early unicellular eukaryotes.[77] Chromothripsis may have provided a way to reshuffle and reassemble genes between their micronuclei (germline) and macronuclei (somatic DNA).[78] Thus, SAM predicts that chromothripsis in cancer represents a reversion to an earlier form of gene sorting and recombination, still practiced by modern ciliates.[79] In an analysis of aneuploidy in cancer, Salmina et al.[79] conclude that *"This cancer life-cycle has parallels both within the cycling polyploidy of the asexual life cycles of ancient unicellular protists and cleavage embryos of early multicellulars, supporting the atavistic theory of cancer."* See also.[80,81]

Oxidative phosphorylation and the Warburg Effect

Eukaryogenesis was marked by the endosymbiosis of alpha-proteobacteria capable of oxidative phosphorylation. This allowed a shift from glycolysis to oxidative metabolism, although glycolysis has been maintained as a backup for coping with hypoxic conditions, and as a mechanism to generate the precursors for macromolecule biosynthesis.

When oxygen is available, normal cells perform oxidative phosphorylation (= aerobic respiration with mitochondria) for energy production. When oxygen is less available (hypoxia), normal cells switch to anaerobic glycolysis. When oxygen becomes available again, normal cells switch back to oxidative phosphorylation. In contrast to this normal behavior, cancer cells engage in "aerobic glycolysis"; they rely heavily on glycolysis even when oxygen is available. This is known as the Warburg Effect[82,83] and is one of the hallmarks of cancer. When cancer cells prefer glycolysis even when oxygen is available, they are behaving like cells that have reverted to their ancient, glycolysis-only origins. Glycolysis (and its many variants) is more ancient and robust than aerobic respiration.[84,85] SAM hypothesizes that the metabolic shift toward glycolysis during cancer progression is an atavistic reversion.

Although this simple story is plausible, the history of atmospheric oxygen is complicated. From 4 to 2.4 Gya oxygen pressure was less than 10^{-7} bar (anoxic). The great oxygenation event 2.4 Gya saw the level increase by 4 orders of magnitude from 10^{-7} to 10^{-3} bar. Yet this is still extremely hypoxic. Only relatively recently, during the Neoproterozoic oxygenation event (~0.6 Gya), did the level rise from 10^{-3} to 10^{-2} bar (which was still hypoxic). It remained so (~10^{-2} bar) until ~0.4 Gya when, during the Devonian, the level increased from 10^{-2} to the 0.2 of today.[86,87] Before ~0.4 Gya our ancestors lived in the oceans. Therefore, it is plausible that the Warburg Effect, instead of being associated with eukaryogenesis ~2 Gya, could be much more recent and correspond to a more extended

evolutionary transition. Note that SAM also predicts that early embryonic stem cells should favor glycolysis over aerobic respiration. It is well-known that early-stage mammalian embryos grow in hypoxic conditions, for example.[88]

The origins of adaptive immunity

Adaptive immunity evolved about ~0.5 billion years ago, over 150 million years between nodes 22 and 21 (~0.62–~0.48 Gya) in Figure 1. Jawed vertebrates (Gnathostomata) have both adaptive and innate immunity while jawless vertebrates (Agnatha) have only innate immunity. These two clads separated about 0.62 Gya (Figure 1, node 22). The transition corresponds roughly to the further differentiation of the proto-hematopoietic cascade into oxygen carrying cells and the cells of the adaptive immune system. Given the relatively recent nature of this transition, SAM predicts that the ability of tumor cells to signal and cooperate with the host's system of adaptive immunity should be lost soon after the onset of tumorigenesis.[4] Likewise, we predict that early embryogenesis depends most heavily on the innate immune system, which does indeed seem to be the case, for example.[32,33,65,89]

Modifications of current phylostratigraphy to improve age resolution

The physiological/cellular systems listed in column 1 of Table 1 are the result of the evolution of complex hierarchies of mutually dependent genetic networks. However, in each of these networks is a still-poorly-understood order in which their parts were assembled and their dependencies evolved. This limits our ability to test SAM in detail. The recent rapid increase in the number of species with known genomic sequences and the assembly of these sequences into trees, has allowed us to estimate gene ages using gene homologies. This technique is called phylostratigraphy. Given the previous success of applying phylostratigraphy to identify a reversionary pattern during tumorigenesis,[13-20] refinement of the methods to achieve improved gene age resolution may enable phylostratigraphy to test the fundamental hypothesis of SAM: that in general the molecular, cellular physiological and phenotypic changes ("hallmarks") seen during tumorigenesis mirror in reverse order the evolutionary transitions of our lineage over billions of years—a timescale much older and much longer than generally recognized by those studying cancer. Thus, we offer the following suggestions to improve gene age resolution.

Use more nodes

The more phylostrata that are included, the better the age resolution. Ideally one would use the full 46 listed in [21], but if this proves computationally intractable, we suggest removing the most recent 10 or 15 nodes from the analysis, because the transformations in cancer progression predominantly involve pre-Cambrian genes. A higher age resolution should be able to investigate more of the details of the unicellular-to-multicellular transition involving the evolution of cell differentiation cascades and hence a step-by-step reversion to "stemness" (Figures 2 and 3).

Choose a subset of nodes strategically

For example, to test the multicellular-to-unicellular reversion, multicellular nodes {1-31} need to be contrasted with unicellular nodes {34-46}. To test the eukaryote-to-prokaryote

reversion, eukaryote nodes {1-41} need to be contrasted with prokaryote nodes {42-46}. To test the reversion of cancer cells to an inability to cooperate with the adaptive immune system, jawed vertebrate nodes {1-21} need to be contrasted with pre-jawed vertebrate and earlier nodes {23-46}.

Use the dates of the nodes, not just the rank order

Molecular clocks have yielded approximate dates (with error bars) for the nodes (Figure 1, column 5 of Table 1 and [21]). Using node dates and including more nodes will yield better gene age resolution. The absolute time and the time elapsed between nodes is more important than node rank because absolute time allows comparison with the dates of environmental changes such as the great oxidation event. Also, using only node rank implicitly assumes that the nodes are equally spaced in time, which they are not. In Figure 1 for example, some nodes are only ~10 million years apart (nodes 23, 24, and 25), while others are 700 million years apart (nodes 41 and 42).

Expand the database

The increasing speed and decreasing cost of gene sequencing is enabling an exponential increase in the number of full genomes available for analysis. This allows a search through more species in each of the two lineages descending from a node. There is a large dynamic range in the numbers of species. For example, there are five extant species of monotremes, 340 species of marsupial and 5000 placental mammals. Particularly for nodes with few species, and for nodes with many parasitic species in which much gene deletion has taken place, it makes sense to use as many species as possible to reduce the problem of genes existing at the node but being deleted during subsequent evolution.[90,91]

Do not conflate nodes unnecessarily

In one analysis, the full genomes of 6 mammals were used without distinguishing monotremes, marsupials and Xenarthran/Afrothere placentals, (node times of ~175, 160, 105 million years, respectively[21]). If it is necessary to conflate nodes for computational reasons, choose the ones that are close together in time. For example, near the 32 species of Lancelet descending from node 23 are two other nodes (24 and 25). The three are dated at 675, 680, 685 Mya. The next deepest node (26) is more than a 100 million years earlier at 795 Mya. That leaves a 100 million years of evolutionary changes that phylostratigraphy cannot resolve. Another triplet of nodes that can be conflated without much loss of time resolution are the nodes (29, 30, and 31) for Parahoxozoa, Eumetazoa and Metazoa at 945, 950, and 955 Mya, respectively. Large molecular clock uncertainties make it possible that these are not actually separate nodes.

Phylostratigraphy is not limited to genomes

In addition to yielding age distributions of cancer-associated-genomes, phylostratigraphy can be applied to cancer transcriptomes, proteomes and (potentially) epigenomes. All four levels of information play into the phenotype. The phylostratigraphy of epigenomes could help trace the evolution of our epigenome and find an evolutionary pattern in what is often neglected and referred to as “aberrant methylation.”

Resolving gene pleiotropy

The chronology of the evolution of phenotypes over billions of years is more complex than a simple linear arrangement of gene ages mapped on to a linear sequence of cancer hallmarks. Two large complications to this simple picture are: What do we mean by the age of a gene? [30,31] and How can we assign ages to phenotypes or cellular abilities when any biological phenotype or cellular ability is based on a hierarchy of old and new genes in an evolving genetic network? It is common that a single protein produced by a gene, has multiple roles in distinct cell types.[92,93] The protein may have originated 2 billion years ago performing function 1. A billion years later it could be co-opted into performing function 2 as well. And then 100 million years ago it could have become part of a network that produces a specific phenotype. Such a gene can then be said to have multiple ages depending on which function is of interest. Thus, gene functional pleiotropy produces multiple effective ages for a given gene depending on which function one is referring to. These complications currently limit phylostratigraphic tests of SAM predictions. However, if homology searches of species trees can differentially weight and target a sequence within a gene that is associated with a specific function, then phylostratigraphy (based on such searches) can identify the multiple effective ages of a gene and reconcile gene family trees with species phylogenetic trees. [30,31]

With these improvements, the age resolution of phylostratigraphy can approach the node separation times shown in Figure 1.

DISCUSSION

Evolution of interactomes

Trigos et al.[17] report results on the loss of coordination between unicellular functions and multicellular regulators. They call the coordinating genes the interactome. The atavistic signature they saw was not a simple re-primitivization to unicellularity. Rather it was a rewiring of the coupling between the gene networks that control unicellular processes from those that control multicellular processes. This phenomenon has a natural explanation within the SAM framework. While the new suppression mechanisms (column 2) were evolving, they were competing against anti-suppression mechanisms evolving at the same time, similar to a predator/prey arms race. These latent anti-suppression mechanisms are what we see emerging in cancer. Further investigation of this and other interactomes can test SAM, since SAM predicts that interactomes are pre-existing organizational structures, not newly evolved adaptive features of cancer.

Different cell types, different cancers

Because of the large number of different cell types in the human body, cancer is sometimes called not one disease, but many. Many normal mature blood cells are not associated with a given organ. The mobility of blood cancers reflects a unicellular mode of life, while solid tumors in some organs are more like dense advanced colonial organisms. Recognizing that the processes of the normal human body are determined by a mixture of old and newly-evolved abilities, and depend on cell type and developmental stage, means that an “atavistic reversion” has different implications depending on which cells are doing the

reverting. Thus, the variation in cell phenotypes (as well as normal phenotypic plasticity) are factors that can obscure the patterns of reversions described here—except in the most advanced cancers where the patterns could become more obvious.

Non-adaptive reversions

Some cancer cells may revert to ancient abilities without having a proliferative advantage over normal cells. These cells will attract scant attention from oncologists. SAM does not claim that all reversions will be adaptive and help cancer cells outcompete normal cells in the body. Rather SAM hypothesizes that all adaptations that help cancer cells to outcompete normal cells are reversions.

Clonal selection for what cancer cells need in order to survive as cancer progresses will affect the order of acquisition of cancer's capabilities. Acquired capabilities may be determined by what happens to be adaptive at a particular stage of cancer progression. Thus, SAM does not necessarily apply to the order in which mutations appear during tumorigenesis but rather the order in which cellular phenotypes appear during cancer progression. During tumorigenesis, the order of appearance of phenotypic reversions will be influenced by selection as well as evolutionary chronology: "…the ecology of the microenvironment of a neoplastic cell determines which changes provide adaptive benefits." [94] However, we are probably dealing with a feedback system in which neoplastic cells play a determinative role in shaping their microenvironment, thereby shaping what is adaptive.[95] Evolutionary chronology may determine the inter-cell signaling and the ability of cancer cells to induce a cellular environment in which their atavistic reversions are adaptive.

The non-genetic recruitment of neighboring cells as collaborators in cancer[96-98] is also a well-known feature of atavisms produced experimentally without a mutational basis. Tissue interactions and cell-cell signaling activate previously quiescent portions of the normal genomes of surrounding cells. In the literature on atavisms this is known as epigenetic integration.[6-8,99,100] A prediction of the atavistic model is that the recruitment of neighboring normal cells in cancer is done in a way similar to the epigenetic integration of experimental atavisms.

Our atavistic model and SAM were primarily developed to explain the vast majority of cancers which are associated with ageing. We have not yet developed the atavistic model far enough to include childhood cancers which are quite different and much less frequent than cancers associated with ageing.

How far back can cancer revert?

How far back phylogenetically can cancer revert to? How would cancer cells evolve if they did not kill their hosts? Would they atavistically revert toward an ever earlier (phylogenetic and ontogenetic) phenotype? Does the genetic instability and aneuploidy of cancer cells progress beyond mitosis to bacteria-like fission? What are the hallmarks of cancer progression after a patient dies? Are there even higher grades of cancer? How undifferentiated can cells get?

Chen et al.[15] wanted to address these questions. They tried to follow and characterize the complete evolutionary history of a tumor by xenografting human-breast-cell-derived tumors through several generations of mice. The expression profiles were found to evolve towards that of embryonic stem cells—the cell type resembling unicellular life.[15] In related work, Xu et al.[81] continued the life of cancer cells in culture. They found changes in the sex chromosomes reflecting atavistic reversions to a unicellular state.

As cancer progresses, do ancient abilities get replaced by even more ancient abilities?

As cancer cells atavistically revert beyond 1 Gya, say to 2 Gya, might they lose their 1 Gya abilities? For example, angiogenesis is an important capability of cancer cells but is not a feature of unicellular organisms, or even early colonial organisms. Vascularization is absent in sponges and corals. The sustained ability to create blood vessels (even disorganized ones) allows the tumor to grow beyond the limitations of passive nutrient diffusion and is one reason why cancer is so dangerous. Vascularization has been present in our human lineage for about 0.7 Gyr, since ~node 25—relatively late in the billion-year unicellular-to-multicellular transition. Therefore, in SAM, we expect the disregulation of angiogenesis to be acquired early in cancer progression. But extending the same reasoning, SAM also predicts that as cancer progresses, the ability to perform even disregulated angiogenesis would be lost. Do some advanced cancers go into remission because their cells lose the ability to perform angiogenesis? Would anyone notice this as a cause of remission? Reversion may be limited by an important constraint: cancer can only revert to phenotypes compatible with cellular survival in a human. Maybe cancer cells can only revert back to early multicellularity since tumors need to remain integrated into the body and remain well-vascularized to be harmful?

CONCLUSIONS AND OUTLOOK

The popular but somewhat vague description of cancer as a reversion to a more primitive evolutionary state has recently been sharpened by the application of phylostratigraphy, which can assign ages to genes. In this paper, we predict that improved phylostratigraphy will reveal systematic patterns of reversion: specific chronological sequences in the onset of cancer hallmarks that mirror, in reverse, the order in which their underlying wiring evolved historically. This sequence is detailed in Table 1. We term this hypothesis the Serial Atavism Model of cancer (SAM). We describe several new predictions based on the unicellular-to-multicellular transition as well as on three other evolutionary transitions that occurred in our lineage: eukaryogenesis, oxidative phosphorylation and the transition to adaptive immunity. We propose several modifications to current phylostratigraphy to improve age resolution and test these predictions. It is unusual in biology that a theory makes such quantitative testable predictions.

Consideration of the evolutionary origins of cancer is not normally taken into account by cancer biologists, but we believe a full understanding of cancer as a biological phenomenon with a deep evolutionary history, and occurrence across most multicellular species,[11] is critical in the search for effective treatments. SAM has many implications for cancer therapy. In [4] we already proposed a target-the-weakness therapeutic strategy based on the atavistic

model, noting that most cancer treatments target the proliferative prowess of neoplasms, which is the most deeply-entrenched and protected property of cells. A therapeutic strategy that depends on the irreversibility of atavistic reversions can take advantage of the difference between the capabilities of normal cells and the reduced capabilities of cancer cells as they atavistically revert in the sequence hypothesized by SAM. We envisage that the elaborations of the atavism theory described here will encourage treatment regimens customized to the specific evolutionary histories of cancer phenotypes.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Abbreviations:

CML	chronic myeloid leukemia
CSC	cancer stem cell
LUCA	Last Universal Common Ancestor
SAM	Serial Atavism Model
UEME	unicellular-eukaryote-to-multicellular-eukaryote

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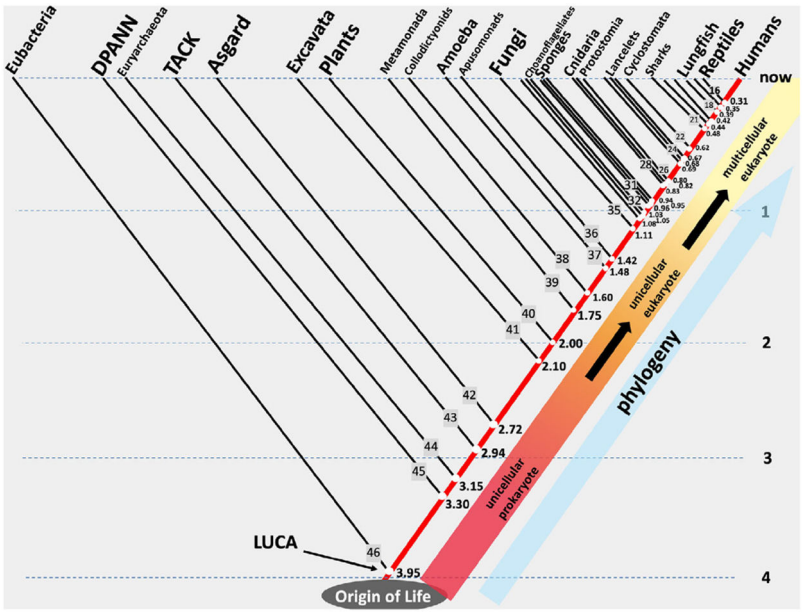

FIGURE 1.

Phylogenetic tree of life on Earth showing the 4-billion-year evolution of our lineage (red line). Humans are at the top right. Our living cousins are listed across the top. Their lineages (thin black lines) diverged from our lineage at nodes labelled 46 - 16 and are marked with white dots. Estimates of divergence times are given in billions of years next to the white dots. For example, humans and reptiles have a common ancestor that lived 0.31 billion years ago. The label “16” next to the node indicates this is the 16th node in the compilation of ref. [21]. Two major transitions are indicated by the black arrows in the orange/yellow diagonal band on the right: the unicellular-prokaryote-to-unicellular-eukaryote transition at ~2 Gya and the unicellular-eukaryote-to-multicellular-eukaryote transition at ~1 Gya. “LUCA” is the Last Universal Common Ancestor of all extant life. For more on these nodes and the major transitions in the evolution of life see [22-24]. Figure modified from [25]

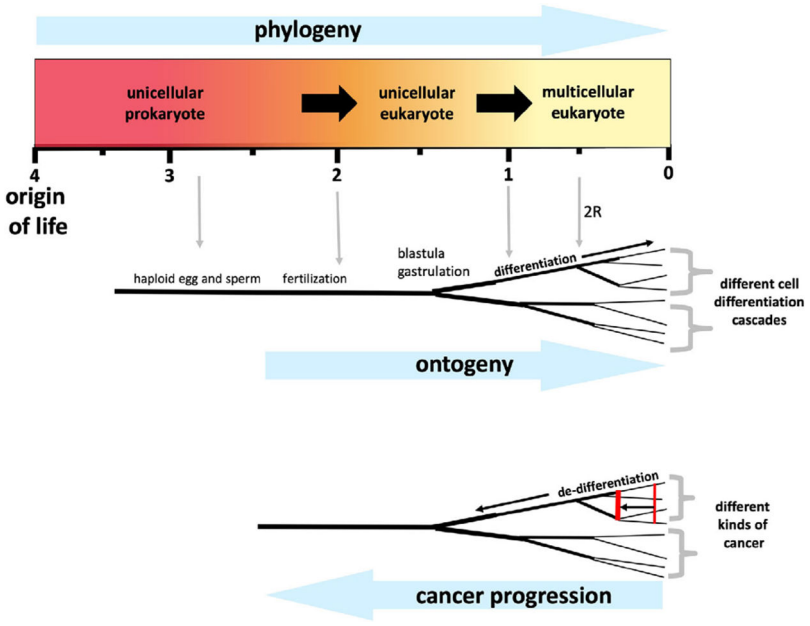

FIGURE 2.

The parallel relationships between phylogeny, ontogeny and cancer progression. Top: the phylogeny of our human lineage (Figure 1) can be characterized by at least two major transitions separated by a billion years: the unicellular-prokaryote-to-unicellular-eukaryote transition about 2 billion years ago, and the unicellular-eukaryote-to-multicellular-eukaryote transition about 1 billion years ago. Middle: the ontogeny of a multicellular organism (embryogenesis and cell differentiation). The vertical grey arrows indicate the relationship to phylogeny. “2R” refers to two rounds of whole genome duplication.[70,71] Bottom: in the atavistic model, cancer progression is an anti-parallel counterpart to ontogeny and phylogeny. The vertical red lines represent an increasingly stem-like maturation block of a differentiation cascade during cancer progression (e.g., chronic myeloid leukemia). This diagram should be relatively independent of organism lifespan under the assumption of allometric scaling of cell differentiation cascades[72]

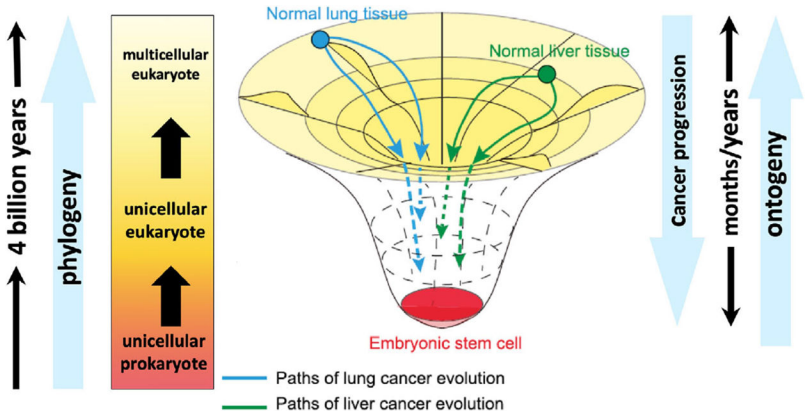

FIGURE 3.

The parallel relationships between cancer progression, ontogeny and phylogeny. Center: as cancer progresses, cancer cells from different organs, lung (blue) and liver (green), converge towards an embryonic stem cell phenotype. In the atavistic model this is the transformation of differentiated cells of multicellular organisms into less-differentiated cells as they atavistically revert to less-regulated, more colonial and unicellular phenotypes. The similar months-to-years timescale and anti-parallel relationship of ontogeny and cancer progression is indicated on the right. Our 4 billion years of phylogeny (Figure 1) is indicated on the left, along with two major transitions: prokaryote-to-eukaryote and unicellular-to-multicellular. The central part of this figure is from Figure 5 from[12], who wrote: *"cancer evolution is a directional process toward a defined cellular destination."* This destination resembles embryonic stem cells, but see[73]

TABLE 1

Hallmarks of cancer progression and their phylogenetic origins[a]

1	2	3	4	5
Physiological/ cellular systems affected in cancer	**Normal abilities lost in cancer**	**Latent abilities gained in cancer**	**Ontogeny: Location and time during normal development when latent abilities are active**	**Phylogeny: Approximate date of origin of column 2 abilities and the corresponding node in** Figure 1
Immunity	Signaling and cooperation between individual cells and the host's system of adaptive immunity. Complete maturation of hematopoietic cells, including the full suite of cells active in the adaptive immune system	Insensitivity to adaptive immunity and therefore freedom from destruction by the adaptive immune system. "avoiding immune destruction"[b]	During embryogenesis before adaptive immunity develops, the embryo/fetus is more dependent on innate immunity[32-34].	Adaptive immunity is absent in cyclostomata/ Agnatha. It has been present in our lineage for ~0.5 Gya, since ~node 21.
Vascularization	Normal well-regulated angiogenesis	Unregulated, rapid and aggressive angiogenesis. The sustained ability to create blood vessels allows the tumor to grow beyond the limitations of passive nutrient diffusion. "inducing angiogenesis"	Trophoblast activity during placental implantation, also embryogenesis, organ formation and in adults, wound healing	Vascularization (organisms with blood vessels) is absent in sponges and corals. It has been present in our lineage for about 0.7 Gyr, since ~node 25. The origin of angiogenesis could be associated with the split of the immune and blood systems.
Cell mobility	Regulated release and adhesion to neighboring cells using E-cadherin, signaling to maintain adhesion. Regulated EMT (Epithelial-to-Mesenchymal Transition) and MET (Mesenchymal-to-Epithelial Transition).	Cells grow independently of tissue anchoring and can aggressively invade neighboring tissues, migrate and metastasize to distant sites. Unregulated EMT and MET. "activating invasion and metastasis"	EMT needed for tissue maintenance, wound healing, normal cell migration during embryogenesis, for example, migration of neural crest cells, trophoblast invasion of uterine walls during placentation. Tissue invasion and displacement to distant sites are normal properties of leukocytes.	Tissue anchoring evolved with colonial eukaryotes (choanoflagellates) about 1 Gya, since ~node 32. Cell migration during embryogenesis in metazoa evolved later, possibly since node 21.
Proliferation	Well-regulated cell proliferation, normal p53 and cell cycle checkpoints, signaling to control proliferation and bring an end to wound healing. Hayflick limit.[35]	Unregulated cell proliferation; self-sufficiency in growth signals, an insensitivity to anti-growth signals, an ability to evade apoptosis and evade signals to senesce. This leads to unlimited replication surpassing Hayflick's limit, relief from cell cycle checkpoints: "wound healing that does not stop." "sustaining proliferative signaling" "enabling replicative immortality" "resisting cell death" "evading growth suppression"	Tissues where rapid cell proliferation is needed, embryogenesis, stem cells, wound healing, tissue maintenance. There are different modes of proliferation during ontogeny, for example, cleavage without growth during blastula formation.	Mitosis originated during the prokaryote-to-eukaryote transition about 2 Gya, ~node 41. The regulation of mitotic proliferation, that is, Hayflick limit[35] evolved much later with the emergence of multicellularity.
Genetics	Normal ploidy, genetic	Aneuploidy, genetic instability. "genome instability"	Stress response, DNA repair, chromosome number variability may be a mechanism to generate variation in offspring.	Chromothripsis evolved in unicellular eukaryotes about 2 Gya, ~node 41. Many other aspects of genetic plasticity, rearrangement and differential repair have evolved since then.
Metabolism	Facultative switching between oxidative phosphorylation and anaerobic glycolysis to deal with periods of hypoxia	Cancer cells shift their metabolism from oxidative phosphorylation to glycolysis even when oxygen is available: the	glycolysis is needed in normal cells under hypoxic conditions such as in poorly vascularized tissues during	The origin of aerobic respiration/oxidative phosphorylation was with the endosymbiosis of mitochondria about 2 Gya, since ~node 41.

1	2	3	4	5
		Warburg Effect. “deregulating cellular energetics”	embryogenesis and in muscles during extreme physical exertion	However, see “Oxidative phosphorylation and the Warburg Effect”

[a] Based on the hallmarks of cancer.[26,36,37] The correspondences between columns 2, 3, and 4 are supported by a vast amount of literature for example[9,28,38-42]. Correspondences with column 5 are inferred from the features of our living cousins in monophyletic clads descending from the nodes in Figure 1.

[b] Red font indicates the wording used in.[26] They recognize “genomic instability” as a hallmark-enabler.