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Reverting to single-cell biology: The predictions of the atavism theory of cancer

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Abstract

Cancer or cancer-like phenomena pervade multicellular life, implying deep evolutionary roots. Many of the hallmarks of cancer recapitulate unicellular modalities, suggesting that cancer initiation and progression represent a systematic reversion to simpler ancestral phenotypes in response to a stress or insult. This so-called atavism theory may be tested using phylostratigraphy, which can be used to assign ages to genes. Several research groups have confirmed that cancer cells tend to over-express evolutionary older genes, and rewire the architecture linking unicellular and multicellular gene networks. In addition, some of the elevated mutation rate – a well-known hallmark of cancer – is actually self-inflicted, driven by genes found to be homologs of the ancient SOS genes activated in stressed bacteria, and employed to evolve biological workarounds. These findings have obvious implications for therapy.

Keywords

Phylostratigraphy; Atavism; Evolutionary ages; Unicellularity; Bacteria; SOS response

1. Introduction

What is cancer? This fundamental question has far reaching consequences in how we manage and treat the disease and yet it remains unanswered despite decades of research. Far from being confined to a few mammalian species, cancer or cancer-like phenomena have been found in organisms across multiple kingdoms in multicellular organisms (Aktipis et al., 2015), suggesting deep evolutionary roots tied to the transition between unicellular and multicellular life. As such, cancer provides a window on the past, giving us insight into how cells are able to reconfigure their information-processing capabilities based on the microenvironmental context in which they find themselves.

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Author statement

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Declaration of competing interest

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The hallmarks of cancer describe the functions that a cell or group of cells must express to become a cancerous tumor, including uncontrolled growth, uninhibited mobility, and resistance to cell death (Hanahan and Weinberg, 2000, 2011). These are traits associated with unicellular organisms, so the onset of cancer represents the breaking of the ancient contract of cellular cooperation that forms the basis for multicellular life (Aktipis et al., 2015). The prevailing paradigm of cancer, referred to as the somatic mutation theory, ascribes the acquisition of the distinctive hallmarks to the gradual accumulation of genomic changes. The changes are normally assumed to be stochastic in nature, with a probability that increases with certain environmental insults or to genetic predispositions that increase the cell's susceptibility to disruptive agents or compromise their damage-repair mechanisms. Support for the somatic mutation viewpoint comes from the fact that most cancers exhibit evidence of genomic alterations/mutations across a range of scales from single nucleotides to entire chromosomes (Li et al., 2020; Rheinbay et al., 2020; Rodriguez-Martin et al., 2020; The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium, 2020). Those tumors with little evidence of genomic alterations at the sequence level often exhibit evidence of disrupted epigenetic modifications, the most studied of which is DNA methylation (Bender et al., 2013; Buczkowicz et al., 2014; Castel et al., 2015; Fontebasso et al., 2014; Mackay et al., 2017; Roy et al., 2014; Schwartzentruber et al., 2012; Taylor et al., 2014; The Cancer Genome Atlas Network, 2012; The St Jude Children's Research Hospital-Washington University Pediatric Cancer Genome Project et al., 2014). Furthermore, in vitro studies of both skin and colon cancer support a model of step-wise transition between normal, pre-malignant, and malignant growth (Fearon and Vogelstein, 1990; Schulz, 2005). The presence of genomic and epigenomic changes in tumors has been the rationale behind the development of "targeted" therapies that are designed to be active only in those cells with specific genomic or epigenetic alterations. However, given the ability of neoplasms to evolve in the host, the emergence of therapy-resistant tumors is a common and almost inevitable outcome, resulting in relapse and eventual death from the disease.

While the association of cancer with widespread genomic and epigenomic changes is not in doubt, the somatic mutation theory of cancer does not provide a comprehensive or deep explanation of the link. It has been useful up to a point, but it suffers from the problem that most oncogenic changes are neither necessary, sufficient, nor context-independent. For example, the first recurrent chromosome translocation documented in human cancers, t(9;22) also known as Philadelphia chromosome (Nowell and Hungerford, 1960; Rowley, 1973) is a necessary and sufficient cause of chronic myeloid leukemia when it occurs in myeloid cells at a particular stage of development. Outside of that stage, it is insufficient to cause disease, and there are multiple reports of individuals with evidence of the translocation in leukocytes but no evidence of disease (Biernaux et al., 1995; Bose et al., 1998; Ismail et al., 2014). Furthermore, the behaviors that constitute the hallmarks of cancer can be suppressed in tumor cells by putting them in a physiologically normal environment (Maffini et al, 2004, 2005; Ricca et al., 2018; Sternlicht et al., 1999; Weaver et al., 1997), resulting in the growing recognition that the tumor genome is only one piece of the cancer puzzle, albeit an important one. What we need is a conceptualization of cancer that accounts for all of the ways the tumor genome can be arranged as well as how the tumor interacts with both the immediate tissue microenvironment and the host immune system, as well as the observation

of cancers that are directly transmissible, e.g. not the result of a viral transformation, but the longer term propagation of clonal tumor cells between animals and across species lines (Metzger et al., 2016; Ostrander et al., 2016).

1.1. Reconceptualizing cancer as an atavism: an old idea

We propose to reconceptualize cancer as a kind of atavism, in this case the reversion to ancestral single-cell behaviors as an inappropriate response to physiological stress and possibly leading to a speciation event. The hallmarks of cancer are not the acquisition of novel behaviors due to genomic mutation but rather the redeployment of ancient, unicellular programs that support survival of the cell at the expense of the host and break the contract of cooperation required for multicellular life. The genomic alterations seen in cancer are the visible evidence of the genome that, on the whole, is no longer wired to support multicellular life but instead has reverted to an ancient logic that facilitates survival of single cells. This perspective frames cancer in terms of evolution, both cellular over the course of carcinogenesis and organismal over millions of years. It puts cancer in an ecological context at both the cellular and organismal levels as well. At the cellular level, the tumor sees the surrounding tissue microenvironment and the host as an ecosystem with resources to exploit and dangers, like the immune system, to avoid. At the organismal level, environmental factors influence not only exposure to potential oncogenic agents but the evolutionary pressures on life history and host cancer defenses as well. Most importantly, this perspective places adaptability and evolvability at the very center of therapeutic development, as they are the basis for tumor heterogeneity, an increasingly recognized defining characteristic of the neoplastic phenotype (Dexter and Leith, 1986; Fidler, 1978; Heim and Mitelman, 1989; Heppner and Miller, 1983; Shackney and Shankey, 1995).

The central idea is not new. Theodore Boveri, an eminent German biologist working with sea urchin embryos at the turn of the 19th and 20th centuries, is often credited with the chromosome theory of inheritance which states that individual chromosomes represent the physical location of unique sets of quantitative phenotypic traits, which we now know as genes. The colocalization of phenotypic traits on individual chromosomes explained the linkage of Mendelian inherited traits. Work on multi-polar mitoses in sea urchins led to his conclusion that each somatic cell needs two complete sets of chromosomes, one from each parent, to function normally (Manchester, 1995; Opitz, 2016). From this work, he also concluded that “the tumor problem is a cell problem,” and cancer would be a “consequence of certain abnormal chromosome constitutions.” He summarized his work on tumorigenesis in his 1914 work, “The Origins of Malignant Tumors” (Boveri, 1914, 2008). His work anticipated many later concepts including oncogenes and tumor suppressors, the development of tumor heterogeneity, and tumor evolution. However, in the context of looking at cancer as an atavism, the importance of his work comes from his central thesis that malignant tumors emerge as the consequence of abnormal chromosomal content brought about by an aberrant mitosis, leading to an irreversible defect that results in the loss of “normal reactions of the cell to its environment and the organism as a whole” (Boveri, 2008). This would lead primarily to the re-expression of the primordial nature of cells, with their propensity to proliferate in an unrestricted fashion. This idea that unrestrained proliferation was an ancient, default trait of cells that was suppressed

in context of multicellularity was common at the time. Boveri was careful to stress that while an abnormal chromosome complement was a mechanism explaining the behavior, the causal factor behind unrestrained cell growth was the permanent disruption of the “normal relationship of a cell with its surroundings” (Boveri, 2008). Thus, we like to think Boveri would have agreed with our description of cancer as an atavism: malignant tumors behave like parasitic single-cell collectives because those pathways are still available within the reaction norm of the current genome. This means that cancer is a concomitant feature of multicellularity.

1.2. General predictions

Identifying cancer with the unicellular/multicellular transition implicates the evolutionary history of the respective gene networks in every aspect of oncogenesis, from initiation onwards. The evolutionary age of genes, measured either as a function of phyla or as a function of time, is a useful marker for this history. As such, gene ages will be a key factor in understanding cancer incidence and progression. Furthermore, we can make very specific predictions about the ages of genes involved in tumorigenesis, how gene age and transcriptional alterations should relate, the connection between the ages of genes and the mutational distribution in cancer genomes, and the manifestation of ancient cellular phenotypes in tumor behaviors. Specifically, we should observe the following:

- Genes that are causally involved in cancer should be older than the emergence of complex multicellularity approximately 600 million years ago.
- Younger genes should be enriched in mutations in cancer
- Cancer should show a transcriptional shift toward unicellularity
- Cancer should employ unicellular responses to cellular and environmental stresses.

1.3. Gene age and cancer: causal relationships

Phylostratigraphy is a method to trace any given gene's lineage through its homology and inferred orthology across species (Domazet-Lošo et al., 2007). Once a gene's orthologous grouping has been established, the species that represents the closest evolutionary link to the last common ancestor assigns a “date” to the gene, either by phylogeny (Domazet-Lošo et al., 2007) or through an actual estimated date (Hedges et al., 2015). This is done for each gene, generating a distribution of either phylostratigraphic groups or gene ages. To look at the role of gene age in a particular phenotype, one can then take the subset of genes thought to contribute to the phenotype and ask whether their age or phylostratigraphic distribution differs substantially from the distribution of all genes for a given species. It is important to remember that phylostratigraphic analysis is always from the point of view of the species in which the phenotype under study is of interest. In the case of cancer, that species is homo sapiens. Phylostratigraphy can be used to test the prediction that genes causally implicated in cancer are, as a group, older than the emergence of multicellularity. One such list of causally implicated genes is compiled and maintained by COSMIC, a highly curated database of genes for which there is reliable evidence of a link with cancer, usually mutational but not always. (Forbes et al., 2015). Whether looking by phylostrata

(Domazet-Lošo and Tautz, 2010) or gene age (Cisneros et al., 2017), COSMIC genes are indeed enriched in genes older than the emergence of complex multicellularity, with most having evolved just prior to the advent of simple metazoan life around 1000 million years ago. It is found that COSMIC genes with recessive phenotypes (i.e. when all copies of the gene in a cancer cell need to be nonfunctional for the phenotype to occur) are indeed enriched for genes with ages that correspond to the epoch of emergence of cellular life (Cisneros et al., 2017).

1.4. Gene age and cancer: mutational patterns

Gene age also provides insights into mutational patterns in cancer. The probability of mutation to occur is not uniform across the genome. It is the result of the interplay of several levels of genomic organization. This ranges from where in the nucleus a locus resides – and therefore how easily accessible it is for both damage and repair to occur – to how much transcription takes place at this location, and whether or not the cell can survive a mutation at that genomic position (Akdemir et al., 2020). This difference in mutation probability across different regions of the genome is itself the result of adaptive evolution. This means that over the course of evolution some genomic regions show little change while others can be “preferred hot-spots” of genomic change. For example, genomes contain regions that show significant homology across species in sequence, gene order, and gene orientation. These are known as homologous synteny blocks (HSBs). Additionally, genomes contain regions of repeated chromosomal rearrangement; these are evolutionarily re-used breakpoints (EBRs), where double-strand breaks leading to structural alterations of chromosomes have repeatedly occurred and have been selected for, presumably because changes involving genes surrounding the break point had a selective advantage for the organism. We would expect that this type of genomic organization might show a relationship with gene ages, and indeed we find one. In humans, genes that are pre-metazoan are enriched in HSBs and excluded from EBRs, while genes younger than 1000 million years, coinciding with the evolution of Metazoa, are enriched in EBRs and depleted in HSBs (Cisneros et al., 2017).

Mutations can be scattered as single events across the genome, but they can also occur in clusters that are located more closely together than would be predicted by the overall number of mutations in the genome. We can dig further into the relationship between mutation, gene age, and genome structure by asking questions about where singleton and clustered mutations are likely to occur and how this differs between normal tissues and cancer. Somatic mutation that took place early in development in normal tissue can be found by looking at non-inherited single-nucleotide variants in individuals without cancer. When we examine mutational load in genes, irrespective of variant status as a singleton or part of a cluster, younger genes are enriched in mutations for both normal tissue and cancer (Cisneros et al., 2017). However, differences appear when we look at where in the genome clustered variants are found. In normal tissue, clustered variants are depleted in HSBs and enriched in EBRs (Cisneros et al., 2017). In cancer, the pattern for clustered variants to be enriched in EBRs and depleted in HSBs remains genome-wide, but at the level of individual genes, clustered mutations are no longer excluded from those genes localized in HSBs. This means that genes normally protected from mutation by virtue of their genomic locations are no

longer protected. Furthermore, COSMIC genes are enriched almost two-fold in clustered mutations, even though their ages skew older and they are more likely to reside in HSBs than other genes (Cisneros et al., 2017). These changes in the pattern mutation within EBRs and HSBs highlight an important point: somatic variants in cancer and normal tissues *are found in different genomic regions*. Why cancer somatic variants are relocated into genes in HSBs is still an open question, but two likely explanations come to mind. One is a reversion of genome maintenance programs to unicellular wiring in response to tumor micro-environmental stress factors. The other is the existence of a recovery bias due to selection moving to the cellular level from the organismal level, i.e. the mutation is tolerated *only* at a cellular level and is never detected when it must be tolerated during embryogenesis and development.

1.5. Gene age and cancer: gene expression

In the early 2000s it became apparent from the genome-wide studies of transcriptomes that gene expression in cancer was different from that of the normal tissue in which it arose. The transcriptomes of tumor cells usually retain enough features of their tissue of origin to identify them, but show signs of aberrant signal transduction, elevated proliferation, and resistance to cell death, all single-cell behaviors. Support for interpreting these changes as a switch toward unicellular gene expression patterns comes from recent work on transcriptional responses to rapid acquisition of doxorubicin resistance (Wu et al., 2015) and phylostratigraphy applied to gene expression data in cancer (Trigos et al., 2017). Wu and colleagues used an in vitro system that generated a concentration gradient of doxorubicin to select for the emergence of resistance and identified from RNA sequencing a set of genes that showed no mutations but nevertheless displayed significant differences in gene expression levels compared to wildtype cells. They further showed that genes older than 1000 million years, predating the emergence of multicellularity, were the source of these expression differences (Wu et al., 2015). The observed differences in gene expression without evidence of mutation indicates that the tumor cells have rewired their genomes to elevate their capacity to deal with environmental challenges such as DNA damaging agents.

Trigos and colleagues performed a systematic analysis of gene expression and gene phylostratigraphy and found that the transcriptomes of tumor cells are markedly skewed towards the two most ancient phylostrata in their analysis, corresponding to genes found in unicellular life. Furthermore, in the case of prostate cancer, the increase in the proportion of the transcriptome coming from ancient genes corresponded to a loss of cellular differentiation as defined by increasing Gleason score (Trigos et al., 2017). In both analyses, upregulation and downregulation of genes of different origins (unicellular, UC, or multicellular, MC) depends upon the cellular pathway. This suggests that reversion is not haphazard and random, but a coordinated and systemic re-establishment of unicellular gene expression patterns. Exploring this further, Trigos et al. found a compartmentalization of correlated gene expression in both normal tissue and tumors, where pairs of either UC or of MC genes were generally positively correlated. This points to a modularity of expression based on gene evolutionary history. In contrast, UC-MC correlations are more negative in tumors than they are in normal tissues. Trigos et al. hypothesize that loss of the cross-talk between UC and MC genes is a key factor in tumourigenesis (Trigos et al., 2017). This is

further supported by their work showing recurrent point mutations in cancer are enriched in the regulator genes linking UC and MC gene subnetworks, while copy number alterations affected downstream targets in regions of the gene regulatory network that are distinctly unicellular or multicellular (Trigos et al., 2019).

1.6. Gene age and cancer: cellular responses

The observation that in cancer there are 15 % more somatic mutations outside of genes compared to those within them, and that recurrent mutations are enriched in early metazoan genes that regulate the interaction between UC and MC modules (Cisneros et al., 2017; Trigos et al., 2019) suggests that the regulation of, and cellular responses to, the extracellular environment are actually the key genomic and transcriptomic alterations in cancer. The rewiring of the genome during tumourigenesis focuses on the regulatory circuit(s) that repurpose unicellular cell behavior to benefit multicellular existence. Cancer is often described in terms of normal cells ‘going wrong’ and being out of control. But the characterization of cancer in terms of ‘rogue cells’ misses a crucial property of multicellular life: the cells of a metazoan organism retain the innate ability to revert to unicellular behavior in a coherent manner under certain stressful conditions. That is, the normal-to-cancer transition is a systematic, and in many cases predictable, transformation of cellular functions, a reversion to ancestral functionality.

One such function is a very ancient unicellular survival mechanism is known as stress-induced mutation (SIM). It is a process by which bacteria increase their mutation rate in the face of environmental stress that becomes sufficiently threatening to induce an SOS response at the same time as they are facing double-strand DNA damage (McKenzie et al., 2000; Rosenberg et al., 2012; Shee et al., 2012). During the SIM process, the repair mechanism of double-strand DNA breaks switches from high-fidelity homologous recombination repair to an alternative pathway that employs the error-prone DNA polymerase, Pol IV encoded by *dinB*. The result of this switch is a trail of self-inflicted damage either side of the double-strand break out for many kilobases, displaying a spectrum of both single-nucleotide variants (SNVs) and amplification events. The upshot of such a dramatic increase in focused, localized mutations (‘hot spots’) is the possibility of adaptation to the challenging environment through random generation of adaptive genotypes (Rosenberg et al., 2012). This propensity of bacteria to evolve their way out of trouble is associated with a distinctive signature, namely, a pattern of SNVs clustering around the site of the DSB with a well-defined decrease in probability as a function of distance from the break (Shee et al., 2012).

In humans, there are orthologous genes to dinB that include Pol κ and Pol η, which are responsible for trans-lesion synthesis in order to by-pass damaged bases during normal replication, and are also employed during microhomology-mediated break repair (Sakofsky et al., 2015). One of the hallmarks of most cancers is genomic instability, in particular a plethora of DSBs that result in ongoing structural rearrangements detected by cytogenetics (Heim and Mitelman, 2015; Mitelman and Heim, 2015; Roschke et al., 2002). It has been reported that SNVs in cancer do indeed display clustering patterns, attributed to the activity of Pol η, but also of the AID/APOBEC family of deaminases (Burns et al., 2013; Lada et al., 2012; Roberts et al, 2012, 2013; Supek and Lehner, 2017; Taylor et al., 2013).

So, do cancers do SIM? Recent work suggest that the answer is yes. Temprine et al. demonstrated that inhibition of MAPK signaling or starvation resulted in the translocation of Pol κ from the cytoplasm to the nucleus (Temprine et al., 2020). Nuclear accumulation of Pol κ increased resistance to the BRAF inhibitor, vemurafenib, in melanoma cells (Temprine et al., 2020). Similarly, Russo and colleagues looked at the role of various DNA repair pathways in response to EGFR or BRAF inhibition in colorectal cancer (Russo et al., 2019). They found that mismatch repair and homologous double-strand break repair pathways were down regulated, while translesion synthesis polymerase was concomitantly up-regulated in cells that acquire permanent resistance to therapy (Russo et al., 2019). Cipponi et al. demonstrated that treatment with non-DNA damaging agents nevertheless increased the number of doublestrand breaks observed in prostate, breast, melanoma, and gastrointestinal stromal tumors (Cipponi et al., 2020), implying that the mutational burden is self-inflicted, consistent with our hypothesis that cancer is (at least in part) a response to stress rather than the product of external damaging agents. Furthermore, in vitro exploration of SIM showed the acquisition of resistance to non-DNA damaging agents was accompanied by an increase in the number of de novo single-nucleotide variants observed in resistant clones compared to the parental lines (Cipponi et al., 2020). The resistant clones paid a fitness cost, however, being slower to grow than clones that were sensitive to drug. While these data are intriguing, none of the above-mentioned studies report the detection of the tell-tale sign of SIM in the DNA, namely, clusters of SNVs characterized by a general decrease in mutation density from the center of a cluster. Such a pattern can be thought of as a cluster “shape,” if one were to plot a histogram of mutations as a function of distance. We did indeed find that clusters in both cancer and healthy somatic tissue show the characteristic pattern, with normal cells showing evidence for a highly regulated process with similarly “shaped” clusters, while cancers exhibited a large degree of heterogeneity in cluster “shape” (Cisneros et al., 2018). We also determined that the action of trans-lesion synthesis polymerases resulted in more SNV clusters than either AID or APOBEC. Significantly, diversity in cluster “shape”, i.e. the distribution of mutation density within the cluster, was a predictor of shorter overall survival in patients with cancer (Cisneros et al., 2018).

Evidence of SIM and adaptive evolution in tumors has profound implications for cancer therapy. The association of cluster shape diversity and survival are further support for the problem of tumor heterogeneity in treatment. Current treatments, devised to be give at the maximum tolerated dose, create strong selective pressures. While resistance is not unexpected, the current paradigm postulates that either the resistant clone is pre-existing, survives the clonal sweep, and then goes on to diversify or it emerges as part of the diversification process after the bottleneck of therapy has eased. Either mechanism gives a window of time between response and the outgrowth of resistant clones and the re-establishment of clonal heterogeneity. Adaptive evolution in tumors means that window does not exist. Clonal heterogeneity and resistance are induced by the treatment at the same time tumors are experiencing bottlenecks that wipe out some level of pre-existing heterogeneity. The stronger the therapeutic pressure, the stronger the selection for highly adaptive cells that can tune SIM in conjunction with other mutational processes to survive unfavorable conditions. This idea can be tested in vitro using both sequencing and standard karyotyping methods to evaluate SIM through cluster shape and heterogeneity, and clonal

sweeps with concomitant cellular heterogeneity by examining the rate of non-clonal (as defined in clinical cytogenetics terms) heterogeneity in cells that survive selection.

How should we rethink our treatment strategies if adaptability is a selected trait? While not strictly an atavistic argument, as it has been made on evolutionary terms alone, the atavism theory supports a re-evaluation of when the complete eradication of tumor is an appropriate treatment goal. Our current therapies do work in a small subset of patients, no matter what the therapy is. We can devise measures of adaptability that allow us to stratify patients into those where current therapies under the “hit it hard” paradigm will work, and those where growth containment rather than eradication is the goal. Concurrently, we can consider treatment regimens that minimize the selective pressure applied by therapy by using dosing that is the least needed to have an effect. In eradication or growth containment, reducing the selective pressure on the tumor is predicted to be beneficial under the atavism theory. Interestingly, experience from agricultural pest management coupled with mathematical modeling suggests that growth containment is a viable option for managing cancer (Cunningham et al., 2018; Gallaher et al., 2018; West et al., 2019). Three clinical trials thus far have been initiated to evaluate this approach (ClinicalTrials.gov numbers NCT03511196, NCT03630120, and NCT0488839).

2. Final comments

The atavism theory of cancer provides an overarching conceptual framework to explain why cancer is pervasive across the tree of life and an inevitable concomitant of multicellularity. It places the evolutionary ages of genes front and center, and posits a systematic rewiring of the genome in a manner that facilitates the expression of gene networks key to unicellular behaviors. In addition, it accounts for the fact that although genomic alterations are a contributing cause of cancer, it is the resulting permanent disruption of normal interactions with the surrounding tissue microenvironment that leads to tumor formation. The atavism theory emphasizes the role of *adaptability* as a selected trait. The theory provides several testable predictions, as well as a shift in perspective with important implications for clinical practice. If tumor cells are primed by their evolutionary heritage to respond to selective pressures through the generation of phenotypic heterogeneity by accessing innate unicellular traits, then a “take no prisoners” approach to treatment risks creating a monster beyond our control.

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