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Stochasticity and determinism in cancer creation and progression

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This review is written by the two of us, a physicist (PCD) and an oncologist (DBA) who first met through a program of grant support from the National Cancer Institute's Physical Sciences in Oncology Center program[1]. Years ago we both read a book called *Plato and a Platypus Walk into a Bar*, in which the authors try to teach the esoteric subject of philosophy through jokes. Sometimes we feel like our conversations are similarly apt for a bar setting, whereby we sit and compare notes on how we view the world and the science that describes it. At times we come to the table with wildly different perspectives given our backgrounds, and challenge one another or at least try to explain things using our own individual terms and see what emerges. Indeed, sometimes what surfaces in these conversations is quite surprising, unexpected, and remarkably informative. These experiences have shifted not only how we work and approach medicine, but also how we ask questions, how we attempt to solve problems, and how we do science.

Cancer is one of the most intensively studied phenomena in biology; with reportedly over a million published papers, yet a full understanding of this syndrome remains elusive. As a result, current cancer therapy – a mix of surgery, radiation and chemical toxins – has changed little in decades. There has been significant progress in the treatment of certain cancers, for example, childhood leukemia, subtypes of breast cancer and adult leukemia, as well as through recent advances in the immunotherapy of melanoma and renal cell carcinoma, and also modest progress in cancer prevention through public health measures. Unfortunately, however, for many common cancer types survival rates overall have improved only modestly or not at all (depending on the cancer subtype). Life extension through therapy of metastatic disease is mostly a rear-guard action against the inevitable, measured in weeks or months rather than years. We have reviewed the present state of affairs in

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Conflicts of Interest

None

[1]In 2009, to help address the problems of cancer research in a transformative way, the National Cancer Institute (NCI) launched the Physical Sciences-Oncology Centers (PS-OC, opso.cancer.gov) initiative. The PS-OC program is a virtual network of 12 research centers, each involving many academic institutions and led by a physical scientist and a cancer biologist or oncologist. The investigators in these centers conduct a variety of integrated research projects aimed at addressing important questions in cancer biology or clinical oncology, broadly organized into four main topics: (i) the Physical Laws and Principles of Cancer, (ii) Evolution and Evolutionary Theory of Cancer, (iii) Information Coding, Decoding, Transfer, and Translation in Cancer, and (iv) De-convoluting Cancer's Complexity.

oncologic care and present a new type of topical review of the field in this manuscript. We have reviewed sets of data in published manuscripts and drew the conclusion that something is missing here. We have made an attempt to describe, using hypotheses and ideas, what is actually taking place in the cancer experiments at a certain level of coarse graining. We attempt to tie together observations by a novel conceptual framework which we present in this review, as well as the therapeutic implications of these ideas.

This dismal state of affairs, in the face of an unprecedented level of financial resources for research and treatment, strongly suggests that we are looking at the problem in an incorrect fashion. Clinically, cancer is recognized as a condition in which a population of cells (neoplasm) becomes partially or completely decoupled from the host organism's normal regulatory apparatus, and develops its own reproducible phenotype characterized by several well-known hallmarks (1). The dominant paradigm is the somatic mutation theory, which regards cancer as primarily a genetic disease resulting from accumulated and incremental mutations (2, 3). It assumes that the same hallmarks of cancer are recapitulated *de novo* in each host by a fast-paced internal Darwinism. Marked similarities in tumor phenotypes and hallmarks across individuals and even across species are loosely attributed to some sort of convergent evolution, without an explanation for why selection pressures operate so similarly in all these independent systems or why an entire suite of hallmarks are co-located within the same neoplasm (reproducibly resulting in similar phenotypes).

The somatic mutation theory has almost no predictive power, its explanations amounting to little more than just-so anecdotes on a case-by-case basis (4, 5). Crucially, it struggles to explain how *random* mutations confer so many co-present fitness-improving modalities. Or, if the underlying mutations exhibit non-random patterns, as some studies suggest (6), the question immediately arises of why the mutations happen to be weighted in favor of those that confer cancer fitness. In the conventional somatic mutation theory, no explanation for fitness-conferring favored mutations is forthcoming, nor is there any suggestion of what the physical source of the implied non-randomness might be. Moreover, it seems paradoxical that increasingly damaged and defective genomes should create a dynamical system with such a reproducible trajectory of clinical stages, from early dysplasia confined to a specific organ to full-blown malignancy and metastatic dissemination to predictable organ locations within the body. Cancer rarely evolves novel functionality, as might be expected from a mutational theory; rather it merely co-opts or accesses, in an inappropriate context, modalities already available to the organism. Significantly, many of these modalities are expressed in embryo development: for example, a less differentiated phenotype than its 'normal' counterpart, cell motility, angiogenesis and tolerance of hypoxia.

The fact that cancer progresses in such an organized, systematic and predictable manner contradicts the notion of rogue defective cells running amok, and suggests instead a deeply-embedded pre-programmed repertoire of activity – a sort of "cancer subroutine" – possibly triggered by mutations but not primarily driven by them. In fact, it is known that cells with the molecular phenotype (i.e., alterations in oncogenes) characteristic of cancer may exist in normal individuals, yet the host is not affected by these cells in a negative way (7, 8). Some DNA changes may be a necessary hallmark of cancer, but clearly they are not sufficient.

The observation that cancer is widespread among mammals, birds, reptiles and fish indicates that this hypothesized cancer subroutine has ancient evolutionary roots dating back at least to the dawn of multi-cellularity. Phylogenetic data also support this observation (9). This observation suggests that cancer may be a form of atavism – a default to an ancestral phenotype – rather than a chance creation *in situ* (10, 11).

Does the cancer subroutine possess a genomic fingerprint? In addressing the question of genomic changes in cancer, it is crucial to distinguish between mutations, where gene *sequences* change, and gene *expression*, where sequences are unchanged but normally silenced genes become switched on (or vice versa). According to the foregoing atavism explanation of cancer, gain-of-function in cancer stems mainly from the inappropriate up-regulation of intact genes rather than the accidental products of damaged genes: i.e. the cancer phenotype is primarily epigenetically rather than genetically derived. In the case of gene expression in cancer, patterns certainly exist. For example, it has been known for many years that cancer reactivates gene expression patterns that play a key role in embryo development (12).

However, it is undeniable that cancer is also associated with elevated mutations and genomic instability (13). How do these mutational changes relate to the cancer subroutine and how could a subroutine's mutational signal be extracted from the overall noise?

It is helpful to distinguish three varieties of mutations:

1. Random damage caused by environmental factors (e.g. ionizing radiation) or copying errors exacerbated by aging.
2. Random collateral damage resulting from cancer cells relinquishing normal error correcting mechanisms that are not needed to run their core ancestral functionality, or which are deliberately disabled as part of an evolutionary SOS response of the sort familiar in bacteria (14, 15).
3. Non-random changes of their genomes actively engineered by cells as a specific response to a carcinogenic threat (for example, (16)).

Changes 2 and 3 should be considered part of a cancer subroutine.

It is likely that cancer involves all three of the above mutational processes, and a successful theory needs to untangle them. Several mechanisms for self-induced *non-random* and even targeted changes (category 3) are known, and have recently been reviewed (17) under the umbrella label of "natural genetic engineering." It is known that mutator DNA polymerases can create specific point mutations in response to stress in bacteria (18, 19). In cancer, where there are specific identical mutations in different hosts that produce gain of function, a category 3 programmatic response also seems plausible (20). Even wholesale changes, such as the Philadelphia chromosome (t(9;22)(q34;q11)), could be a systematically "engineered" response by the cell to a threat rather than the result of random damage.

A useful analogy is a genie in a bottle, with the genie playing the role of the cancer program and the confining bottle representing the body's, as yet poorly understood, regulatory apparatus (including tumor suppression strategies). The bottle may be shattered in many

ways (mutations caused by radiation damage, hypoxia, carcinogens, inflammation, stromal environmental changes, etc.) but, once released, the genie executes its agenda deterministically by accessing ancient, highly conserved, deeply entrenched and well-protected genetic pathways that control basic multicellular function like development, tissue regeneration and immune response.

In discussing cancer genomics, it is important to distinguish the concepts of origin, cause and trigger. A so-called driver mutation may not actually drive carcinogenesis at all, but merely trigger it, the real driver being the deeply embedded cancer subroutine. To use an analogy, if a computer issues a “run” command for a subroutine that outputs X, the real cause of X is the subroutine, not the run command. A useful illustrative example is provided by the recently reported conserved mutational signatures across more than 7,000 cancers corresponding to underlying etiology in many of the cases, such as tobacco, ultraviolet radiation induced or age of onset (21). Which of these patterns of change are actually causing cancer and which are in fact consequences of a programmatic response (cancer subroutine)?

Whatever the mix of categories 1 to 3, the genetic instability associated with cancer progression will, by definition, offer the opportunity for a selection process to operate, leading to therapeutic resilience (22). But an uncritical extrapolation of neoplastic Darwinism as an explanation for *all* the properties of cancer rests on an inappropriate analogy with Germ Theory (23) and the evolution of bacterial resistance to antibiotics. Cancer is (mostly) a noncommunicable disease, so evolution must re-discover the same properties *de novo* in each host. The pool of genotypes is thus confined to a single host, whereas bacteria, which travel between hosts, can call upon a vast reservoir of genotypes for selection to act on. Germ Theory states that once you identify the organism responsible for the disease you will have a basis for treatment. Cancer though, being a complex system, cannot be successfully targeted solely by understanding its genomic alterations or the individual cancer cell; rather an understanding, or modeling, of the complex emergent system as a whole (the cell, the tumor and its host), will be necessary.

Finally we turn to the therapeutic implications of the alternative view being presented here. Most descriptions of cancer progression focus on the proliferative aspect. It is well known that the tumor burden *per se* can usually be successfully reduced by a variety of clinical interventions – surgery, radiation and drugs – but that for metastatic cancer this approach rarely eliminates the disease completely on account of the phenotypic changes resulting in advancing malignancy. By concentrating on gain-of-function properties, such as the aforesaid proliferation, therapeutic strategies typically target cancer’s strengths. But by defaulting to an ancestral phenotype, cancer cells lose more recently evolved functionality. This loss of function may represent the Achilles’ heel of cancer, and therapies designed to target cancer’s weaknesses may offer a more hopeful and unique alternative for the future (24).

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