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Paradoxes in Carcinogenesis: There Is Light at the End of That Tunnel!

Ana M. Soto and **Carlos Sonnenschein**
Department of Anatomy and Cellular Biology, Tufts University School of Medicine, Boston, Massachusetts

Abstract

The exchange of opinions motivated by Dr. Baker's article "Paradoxes in carcinogenesis should spur new avenues of research: An historical perspective" illustrates the reasons why the field of cancer research is stuck in a dead end. This paralysis presents a rich opportunity for philosophers, historians and sociologists of science to decipher the whys of this impasse. On the strictly biological front, we suggest to reinstate in cancer research the time proven practice so productive in the physical sciences of discarding wrong hypotheses and theories. We share the suggestion by Dr. Baker to stop trying to unify the two main theories of carcinogenesis, i.e., the Somatic Mutation Theory (SMT) and the Tissue Organization Field Theory (TOFT) because they are incompatible. Dr. Baker suggests breaching the impasse by investing in paradox-driven research. We discuss the barriers to the implementation of this novel strategy, and the significant impact that this strategy will have on knowledge at large and its application for the prevention and cure of cancer.

Keywords

cell proliferation; hallmarks of cancer; organicism; proliferative quiescence; reductionism; "tissue organization field theory"

Introduction

Stuart Baker's article "Paradoxes in carcinogenesis should spur new avenues of research: An historical perspective" is of interest not only to biologists, but also to philosophers, historians, and sociologists of science. On the one hand, there is the scientific focus of the article, which points to the state of cancer research and ways to overcome the impasse generated by the Somatic Mutation Theory (SMT), a 100-year-old theory that envisions understanding cancer at the cellular level of organization; according to this theory, cancer is a problem of the control of cell proliferation caused by mutations in genes that regulate this function. Additionally, the SMT considers that the default state of cells in metazoa is proliferative *quiescence*; this means that even when exposed to excess nutrients metazoan cells will not proliferate unless they are stimulated. The SMT is being assailed by an ever increasing number of experimental results that contradict its premises.[1,2] On the other hand, there is the broad repercussion of a trend observed in cancer research of refusing to reject hypotheses, a practice that is inimical to the development of scientific evidence.

Address correspondence to: Carlos Sonnenschein, Department of Anatomy and Cellular Biology, Tufts University School of Medicine, Boston, MA, carlos.sonnenschein@tufts.edu.

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What to Do When Data and Hypotheses Do Not Agree?

According to evolutionary biologist Francisco Ayala, hypotheses' testing is of utmost importance. In his own words, "the explanatory hypotheses provided by science must be genuinely testable, and therefore, subject to the possibility of rejection." From physics to biology, the refutability of hypotheses and theories has been a central component of the practice of science, a subject developed by the philosopher Karl Popper who defined the concept of hypothesis "falsifiability" as a more stringent practice than their validation or verification, which he deemed impossible. Another philosopher, Imre Lakatos addressed the same issue by proposing the concept of "research programs"; these would contain a set of hypotheses that would lead researchers to the stage where the theory becomes testable. In Lakatos' view, programs are progressive when alterations made to render them more realistic generate a new prediction, whereas regressive programs are those that resort to *ad-hoc* modifications that result in no new predictions. In our view, the SMT program is regressive because the *ad-hoc* additions increase neither predictability of outcomes nor an increasing understanding of carcinogenesis.[3,4]

Hypotheses and theories play a central role in cancer research regarding the practitioners' choice of a research program. However, hypotheses rejection is seldom practiced: a given claim and its opposite happily coexist. Most researchers in this area take contradictions as a manifestation of the complexity of the problem being studied. This practice is illustrated by the fact that when presented with alternative theories to the SMT many cancer researchers systematically try to reach a synthesis at all costs, and treat contradictions as an integral part of complexity. This situation, which we witness systematically, at every seminar on this subject, is evidence of how disruptive is the topic of cancer theories that challenge the SMT.

Dr. Baker has faced the call for amalgamating the SMT and the Tissue Organization Field Theory (TOFT) into a "compromise theory" rigorously and scholarly, first, by showing that both theories are irreconcilable due to their opposite premises, and second, by exposing and analyzing paradoxes that cannot be resolved by the SMT without the help of *ad-hoc* additions. To remedy this problem, he suggests shifting resources from technology-driven research to a paradox-driven one. By doing so, "the incompatibility between TOFT and SMT presents an opportunity for new, disruptive, experiments that can move cancer biology forward." Consistent with Dr. Baker's recommendation is our own: reconciling these paradoxes should lead to the rejection of failed hypotheses related to carcinogenesis, which can then move the science forward.

Paradox-Driven Cancer Research Is Disruptive: It Forces the Practitioner to Make Theoretical Commitments

Dr. Baker stated that paradox-driven cancer research "begins with the premise that there are fundamental aspects of carcinogenesis that need to be understood before a major progress can be made." Indeed, results that are paradoxical from the perspective of the SMT, in Dr. Baker's viewpoint, can be explained by an alternative theory, the TOFT. This does not mean that all paradox-driven cancer research requires the adoption of the TOFT, but suggests instead that it is necessary to challenge the very premises of the SMT by proposing alternative theories in which the paradox can be reconciled. Theories are very useful tools because they organize knowledge and construct objectivity. Choosing the premises to be adopted for constructing a theory is a difficult task, because the body of data available to the researcher always shows inconsistencies, contradictions, and exceptions. Choosing to trust one set of data over another, or to adopt one premise over others, is subject to a reasoned, though sometimes intuitive, decision. But, after all, uncertainty is the daily concern of scientists. However, once the choice of postulates is made, they are accepted as being "true."

The practice of hypothesis-testing eventually will decide whether the postulates were sound. A good example of both postulate and dataset choice is provided by Kepler's work, who began by placing the sun at the center of the planetary system with the planets' orbits as a series of heliocentric spheres. Later on, when he decided to use only Brahe's data on the position of the planets to describe their motion around the sun, he found their orbits to be elliptical. Had Kepler considered all available data, he would have found it impossible to fit them into any coherent model.

Dr. Baker uses the TOFT as an example of a theory that provides explanations for results that are paradoxical from the SMT perspective. Thus, the TOFT can be used as a model of the disruptive type of theory that may guide research into paradox-driven research because its premises are irreconcilable with those of the SMT.

The TOFT as an Example of Disruptive Science

The first premise of the TOFT posits that carcinogenesis, like morphogenesis, takes place at the tissue level of biological organization. A key feature of morphogenesis is the morphogenetic field, a group of cells dynamically responding to mechanical, electrical, and biochemical gradients. Chronic abnormal interactions between the mesenchyme/stroma and the parenchyma of a given morphogenetic field would be responsible for the appearance of a tumor. The second premise states that the default states of all cells are *proliferation* and *motility*. A corollary of the TOFT is that carcinogenesis is a reversible process, whereby normal tissues in contact with neoplastic cells may normalize the latter.

Both premises and the corollary of the TOFT are disruptive: the first because, if carcinogenesis occurs at the tissue level of biological organization, it implies that all cancer research done in 2D cell culture containing a single cell type, like those on transformation, that were central to the SMT, are invalid. From this perspective, the only adequate models for the study of carcinogenesis are whole organisms and 3D culture surrogate models that closely resemble the normal architecture of tissues and organs. Because the TOFT posits that carcinogenesis ought to be studied in the context of morphogenesis, its research program includes mechanical forces and electrical fields as determinants of shape. The second premise is equally disruptive because it claims that growth factors are not a plausible entity, since it is impossible to stimulate cell proliferation if all cells are endowed with a constitutive ability to proliferate. The real issue is how does the organism keep cells from proliferating by the diverse means of tissue organization (cell–cell interaction, mechanical forces, electric fields, etc)?[1]

How Would Cancer Research Change If Paradox-Driven Research Is Fostered?

Turning the focus of cancer research towards the exploration of the paradox-driven topics suggested by Dr. Baker will necessarily change the strictly deterministic, bottom-up (from molecules/genes to cells, to organs, to organisms) way of thinking that has dominated biomedical research since the advent of the molecular biology revolution. During this period, there has been one privileged causal entity: the gene. Philosophers as well as biologists raised criticisms about the limitations of this way of thinking.[5–10] Bringing microenvironmental cues by way of morphogenetic fields and morphostats as main actors in carcinogenesis implies the adoption of an organicist view, whereby bottom-up and top-down causation coexist. Accordingly, the organism regains its physicality and historicity, long lost by the adoption of concepts borrowed from computer sciences, such as information, program, signal, etc.[10] Metaphors from computer sciences taken outside their proper context have hindered the advance of biological research.

As suggested by Dr. Baker in his call for more research on morphostats, studying carcinogenesis in the context of organogenesis, tissue remodeling, tissue repair, and healing may resolve some of the paradoxes mentioned in his paper. In this context, carcinogenesis as a tissue-based phenomenon, carcinogenesis would not be an autonomous discipline, but a sub-discipline within developmental biology. The technology required to explore the subject would aim at capturing the four-dimensions of the living, including the various modes of live microscopy which generate data that can be analyzed using sophisticated quantitative mathematical tools. Additionally, systems biology opens up the use of mathematical modeling and computer simulation, not only as heuristic approaches but also to provide understanding by way of rejecting failed hypotheses. The former is illustrated by the generation of models that reveal the plausibility of a given hypothesis, for example, the disruption of morphostat gradients.[11] Also, the generation of counterintuitive *in silico* results may inspire new 'wet' research for both model validation and hypothesis testing as illustrated by a challenge to the widely accepted hallmark of cancer that assumes that cancer cells actively evade cell death.[12,13]

Finally, contrary to the implication of the SMT that cancer cannot be reversed, research based on tissue organization carries the optimist bent that cancer can indeed be reversed as illustrated by a copious experimental literature and a less abundant but no less real clinical casuistic observed in breast, prostate cancers, and particularly regarding neuroblastomas.[14,15] Thus, exploring these tissue interactions is a sound research program towards the prevention, normalization and cure of cancer.

What Are the Major Barriers That Impede Paradox-Driven Research and How to Overcome Them?

As suggested by Dr. Baker, the main barrier is the meager allocation of research funds to paradox-driven research. In view of the failure by the SMT to explain and "cure" cancer, funding agencies and philanthropies claim that they are willing and ready to fund out-of-the-box approaches. However, it is the technology-driven, genetic, reductionist approach to cancer that gets the bulk of the research funds. The good intentions of funding agencies are systematically neutralized in the process of choosing experts to participate in review panels; the most qualified grant reviewers, are those recognized by their past published track-record in elite journals (in the SMT domain), and are for the most part supporters of the *status quo*.[16] This indicates that to finance paradox-driven research, funding agencies should consider transferring to their officers the decision power to select which proposals to fund, while overcoming the impact of a peer review process that perpetuates the status quo.

The second barrier promote paradox-driven research is the above mentioned tendency to amalgamate incompatible hypotheses that has plagued cancer research. This is probably even more difficult to solve than the financial barriers discussed above. Science tends to correct itself, but it may take a significant period of time to bring back to biology a sense of the organism and its complexity, to learn again that explanations are of a multilevel nature, and that "the gene" does not hold a privileged causal role. This may require adopting a humble attitude to look into history and philosophy, areas of knowledge that were an integral part of the formation of biologists of yore, the ones that provided the founding concepts of our discipline.

Finally, we foresee that once the financial barriers are removed, a wave of novel approaches will by themselves suggest a fruitful research program to follow. A cursory analysis of research trends during the 20th century suggests that researchers are good at "following the money." Thus, we are optimistic that if significant funding is earmarked for paradox-driven research, the promises of alternative theories of carcinogenesis will have a chance to be

fulfilled. In the meantime, cancer researchers may consider embracing the complexity of the organism, appreciate the biophysical and biochemical processes that underline its functions, and avoid using metaphors, such as program, information and signal which by trying to equate organisms with computers hinder the understanding of biology.[9,10,17]

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