Perspective

Cancer Research

The Death of the Cancer Cell

Carlos Sonnenschein and Ana M. Soto

Abstract

For a century, the perception that there are qualitative differences between a normal cell and a cell belonging to a tumor has dominated discussions aimed at explaining cancer. However, an analysis of the experimental evidence suggests that individual normal cells and individual cancer cells share the same two fundamental behavioral properties, namely, proliferation and motility. Each individual cancer cell carries no recognizable molecules or structures that make them consistently distinguishable from normal cells. Herein, we argue that the differences between normal and cancerous states are instead identifiable at the tissue level of biological organization, and therefore, the search for identification of a cancer cell should be abandoned. *Cancer Res; 71(13); 4334–7. ©2011 AACR.*

Introduction

For the past century, the question "what is the difference between normal and cancerous tissues and cells?" has been of interest to experimental biologists, medical practitioners, the media, and the public at large. The implication of this quest has been that, indeed, there are objective differences between a normal and a cancer cell whereby the latter has been able to "create" a qualitative novelty distinguishable from that of the repertoire of a normal cell. Here, based on a critical review of the cancer research literature, we argue against the merits of keeping the concept of "the cancer cell" alive.

Background

The currently prevalent somatic mutation theory of carcinogenesis and metastases (SMT) explicitly assumes that cancer is a disease centered at the cellular level of biological organization (1). It further claims that cancer represents a problem of control of cell proliferation and/or cell differentiation. In a recent extended update of their 2000 evaluation of what they called the Hallmarks of Cancer, Hanahan and Weinberg reinforced this interpretation from the selected data they reviewed (2) while making more explicit the participation of the microenvironment in carcinogenesis. However, in their view, the role of the microenvironment is subservient to that of the original mutated cancer cell. In other words, consistent with their previous publications, they still unambiguously claim that cancer cells recruit stromal cell types which in turn would enhance the neoplastic phenotype of the epithelial mutated cell.

In the 2% of germ line–inherited neoplasms, a mutation is present in all the cells of the organism suggesting that it plays a causal role by providing a field effect. Although much can be said about them, we are not dealing here with this subset of cancers. Instead, given that about 98% of clinically detected cancers are of the "sporadic" variety, and of these, 90% are categorized as carcinomas, under the aegis of the SMT, the epithelial cancer cell becomes *the cell* that is the target of carcinogens and therefore the one in which those assumed differences should eventually become obvious. Thus, discrete qualitative differences such as its shape, its size, its tinctorial properties, and the way it divides and/or moves should distinguish it from those of a normal counterpart.

Despite redoubled efforts to find those differences, they have remained elusive for over a century now. Shortly after an alleged singularity in a putative cancer cell is proposed, the same singularity is found in normal cells during the course of the normal development of the organism to which they belong. The repeated failure to identify those anticipated singularities might be a reflection of the adoption by researchers of mistaken premises about the level of biological organization at which cancer originates. This is the gist of what, in 1962, Smithers concluded in a commentary entitled "An attack on cytologism" (3) in which he argued that cancer ought to be studied as a problem of organismal disorganization and not as a *cell-based* disease. Smithers' criticisms and similar ones that preceded and followed his have been ineffective so far in discrediting the majority view that cancer is a *cell-based* disease. In fact, on the one hand, considerable resources are being invested to finally link those elusive mutational events in that single cancer cell with cancer phenotypes to vindicate the SMT, whereas on the other, *ad hoc* options are being offered to reconcile the SMT with the undeniable role played by the microenvironment on the putative single cell that by accumulating an undetermined number of mutations should morph into the cancer cell.

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To circumvent the heterogeneity of tumors, microdissection techniques have been used to collect tumor cells which then were processed for whole-exome sequencing to identify mutations aimed at aiding in patient prognosis and for prioritizing patients for cancer treatments (4). Others are now using ever more sophisticated molecular biology and computational techniques that allow for the analysis of the genome of single cells. From these data, inferences were drawn about the type and number of mutations that, putatively, are causally responsible for the carcinogenic development and tumor metastases (5). These contributions which still argue for a cell-based origin of carcinogenesis deserve a much more detailed, critical analysis than the one offered here. Notwithstanding, these strategies are applied to fully developed neoplasms, and thus, they are unlikely to shed light on the events that initiate carcinogenesis (6). Theodor Boveri, the originator of the SMT, stated almost 1 century ago that we are limited by the impossibility of observing a neoplasm in *statu nascendi* (7). This assertion remains true today.

Cell Proliferation and Motility during Development and Carcinogenesis

Despite the crucial importance that the control of cell proliferation has in normal development and in carcinogenesis, its role in these processes remains a controversial topic, probably because of the different meaning that "the control of cell proliferation" elicits in the mind of researchers as reflected in the literature. When we refer to the control of cell proliferation, we mean to address the question—Why would a cell enter the cycle to generate 2 daughter cells? Instead, the great majority of researchers in this field refer to "the control of cell proliferation" by dealing with the question—Which are the myriads of biochemical and biomechanical steps that a cell has to conduct to generate 2 daughter cells? This latter view would be equivalent to asking the question, how does a cell proliferate? The current majority view as represented in textbooks and commentary posits that *proliferation* is the default state of prokaryotes and unicellular eukaryotes but that *quiescence* is, instead, the default state in animal cells (8–10).[1] However, data collected using hormone target cells (11), stem cells (12), and lymphocytes (13), as well as evolutionary theory consistently favor the interpretation that *proliferation* is the default state of *all* living cells (7).

Historical precedents help us in sorting out who proposed what, when, and whose arguments, regardless of their merit, prevailed during earlier periods. The narrative of the pioneers of tissue culture techniques at the beginning of the 20th century was instrumental in introducing the distorted view, later adopted by those siding with the SMT, that *quiescence* was the default state of cells in Metazoa (7). In this context, François Jacob noted that nature is not an engineer but a tinker (14), the implication being that with the emergence of multicellularity, the default state of cells must have remained unaltered and that the novelty in controlling cell proliferation was the appearance of cell proliferation inhibitors (11). After all, the cell-cycle machinery charged with generating 2 daughter cells has remained virtually unchanged from unicellular eukaryotes to cells in Metazoa (9). Thus, a plausible conclusion drawn from the available data could surmise that *quiescence* in Metazoa is actively induced and/or inducible (7, 12, 13)

Like proliferation, motility is a constitutive property of *all* cells and, therefore, it can only be inhibited (15). Cells from the 3 embryonic layers exercise motility during early development. During postnatal life some cells, such as the wandering cells in the connective tissue also move. Even normal epithelial cells stream at variable speed from their "birth" to their "death" locations (16). In addition, cells move following disruptions in tissue architecture generated by wounds. During incipient and advanced states of carcinogenesis, times at which metastases are generated, cells also move. Thus, motility in cancer cells does not represent a newly acquired property but the restoration of an ancestral, intrinsic cellular condition.

As an alternative to the prevailing cell-based perspective adopted by the SMT, some researchers have concluded that carcinogenesis is equivalent to development gone awry (17). From this perspective, normal and cancer development would belong to the *tissue* level of biological organization (18). In the most frequent classes of epithelial neoplasms, that is carcinomas, the parenchyma is an epithelium. The repeated demonstrations of the reversibility of the neoplastic phenotype when parenchymal cells isolated from neoplastic tissues are placed in normal ones points to the contextuality of cellular phenotypes, and thus to the lack of intrinsic differences between individual normal and cancer cells (19–22). Thus, cancer would be the result of a faulty reciprocal interaction between the parenchyma and stroma.

What Went Wrong?

During the second half of the 19th century, German pathologists diagnosed cancers while using light microscopes, comparable to those used today. They then suggested that cancer was a *tissue-based* disease and, separately, that the default state of cells was *proliferation* (11). At the beginning of the 20th century, the advent of gene-centric research imperceptibly allowed the introduction of a reductionist rationale that encouraged finding phenotypic differences between the normal and the cancer cell (23). Ever since, this search was conducted by adopting a "bottom-up" strategy. The more that was learned about the structural complexity of the cell, the more distant the perceived "bottom" became. Thus, while Theodor Boveri was proposing the theory that cancer was due to chromatin rearrangements within a single cell (7), starting in the 1960s until today, genomic somatic mutations (point mutations, deletions, translocations, etc.) and so-called epigenetic changes (DNA methylation and posttranslational modifications of histones) in that fateful original cancer cell

[1] By default state, an evolutionarily relevant subject, it is meant the state at which a cell will proliferate, or remain quiescent, in the presence of excess nutrients.

became the target of the increasingly elusive explanatory "bottom" (6;24;25).

A number of circumstances conspired against accepting the evolutionary relevant premises implied by the German pathologists (23). Regardless, these scientific miscues resulted in both positive and negative outcomes. Among the positive ones can be cited the staggering amount of knowledge accumulated at the cellular level of biological organization which includes all the biochemical and structural descriptions of cell types, their organelles, their transcriptional and translational quirks, ever expanding signal transduction pathways and networks. Explicitly, one of the declared aims of this decades-old strategy was the identification of those anticipated differences between the normal and the cancer cell. That much can be gleaned from a comment by the famed British scientist John Cairns, who stated,

. . .Biology and cancer research have developed together. Invariably, at each stage, the characteristics of the cancer cell have been ascribed to some defect in whatever branch of biology happens at the time to be fashionable and exciting; today, it is molecular genetics. (26).

Despite the monumental effort already displayed, so far, no qualitative differences have been described between a normal and a neoplastic cell, an assertion now extended to the presence of somatic mutations (27) and aneuploidy in normal cells *in vivo* (28). Nevertheless, judging by the headings in the table of contents of most cancer research journals and textbooks on the biology of cancer, the search for those distinctive differences between normal and cancer cells continues unabated (8).

Is It Time to Consider Alternatives?

An animated controversy among cancer researchers is raging on whether the premises they adopt to collect and interpret cancer data determine the soundness of the conclusions they draw. Supporters of the SMT respond to this controversy by highlighting the anticipated promises of genomic research through a massive sequencing effort of the genome of thousands of cancers and the "mining" of vast data sets (6). This gargantuan effort is overtly aimed at improving the diagnosis, prognosis, and treatment of cancers through what is called translational patient-targeted research. However, a rigorous analysis of these data reveal wide gaps in explaining carcinogenesis and on prospects of clinical relevance (29).

Returning to the seminal argument by the SMT of whether one or many mutations in the genome of a single epithelial cell is responsible for the carcinogenic process, those siding with this theory are admitting either by commission or by omission that no such mutations have been identified so far. Instead, they have offered *ad hoc* scenarios (i.e., that mutations are instead lodged in neighboring stromal cells, that the microenvironment sends either "wrong" signals to said cell, or that the prospective cancer cell lacks the ability to read correctly those at times stimulatory, at others apoptotic, signals, etc.). More often than not, recent tendencies in this regard require that, in addition to the above-referred SMT premises, carcinogenesis include the heavy involvement of the tissue components surrounding the cancer cell niche (2).

Finally, one wonders whether alternative premises and research programs to those offered by advocates of the SMT might now be appropriate when dealing with approaches to cancer research (30) and its applications to the clinic and public health at large (29).

What kind of change can be anticipated if a paradigm switch is adopted? The novel approach in explaining carcinogenesis is anchored on 2 distinct premises: the first posits that *proliferation* is the default state of all cells and the second proposes that cancer is a *tissue-based* disease. These are the premises of the Tissue Organization Field Theory (7, 11). What consequences this proposed switch may have on the overall agenda to unravel the cancer puzzle and on improving the outlook for more rationale management of cancer patients? In the important realm of experimental cancer research, the proposed change would mean a switch from a subcellular, gene-centric approach to a *tissue-based* organicist one, in which a combined top-down and bottom-up strategy would include systems biology components (18;31). From a public health standpoint, one would anticipate a change in cancer public policy that would highlight the underappreciated role of the environment in the causation of cancers and the importance of prevention of exposure (32). In the long run, this conceptual and experimental switch might generate a more rewarding return on investment than the one based on the century-old SMT.

Conclusion

Taking into account the century-old failure to pragmatically characterize features in a cancer cell that would identify it from a normal one, it would be now realistic to finally declare the formal death of "the cancer cell." The interpretation of the staggering amount of data collected during this period is consistent with this suggestion which concurs with that already made about 5 decades ago by Smithers (3) and by others since (7, 17).

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No potential conflicts of interest were disclosed.

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