COMMENTARY

Cancer Metastases: So Close and So Far

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Abstract

Metastases are tumors that develop at a distance from their primary origin and are responsible for the death of 90% of cancer patients. For over a century the notion of seed (migrating cells) and soil (the locus where those cells anchor) provided an accurate account of which were the protagonists in their genesis. Despite aggressive efforts to unravel the dynamics involving migrating cells and the niche in which they anchor, explanations of this process remain ill-defined and controversial. The controversy is generated by the different premises that researchers adopt to integrate the vast amount of data collected at different levels of biological organization. The so-far hegemonic theory of cancer and its metastases has been the somatic mutation theory (SMT) and a number of its variants: They consider that cancers and their metastases represent a cell-based, genetic and molecular disease. This interpretation has been challenged by the tissue organization field theory (TOFT), which considers instead that cancer is a tissue-based disease, akin to development gone awry. In this Commentary, the merits of both theories are compared now in the context of metastases. Based on the epistemological shortcomings of the SMT and the acknowledged failure of therapeutic approaches based on this theory, we conclude that TOFT explains comprehensibly carcinogenesis and the appearance of metastases.

Metastases are defined as secondary tumors that develop at a distance from their primary originators; they are the cause of death for 90% of cancer patients (1). Much has been written and done in the field of cancer metastases since Stephen Paget's seminal work in the 19th century that established the notion of seed and soil (2). Notwithstanding, despite concerted theoretical, clinical, and experimental efforts, the prevailing consensus is that metastases are not explained accurately, and, more importantly, they are far from being successfully managed (3–5).

This widely acknowledged failure is not for lack of trying. Both epidemiologic and experimental evidence confirm the consensus that metastases remain an obscure subject. Buttressing this assessment, I. J. Fidler, an acknowledged pioneer in the field, recently surmised the feelings of most expert contributors to a multi-author issue of *Seminars in Cancer Biology* when he candidly declared that "The field is open!" (6). Encouraged by Fidler's implicit invitation to contribute to the resolution of the cancer metastases puzzle and by our own bench experience, we will be comparing views on this subject, first from the perspective of the somatic mutation theory (SMT) plus its variants (7–11) and next from the tissue organization field theory of carcinogenesis (TOFT) (12–14). In order to propose changes in perspective, we will begin by outlining which are the premises adopted by these two main distinctive theories.

Under What Premises Have Explanations of Metastases Been Interpreted?

Pathogenetic explanations of metastases have encountered comparable obstacles with those suffered by the carcinogenetic process of primary tumors (12). Briefly, SMT considers that cancer is: 1) a cell-based, and thus clonal, disease and 2) that the default state of cells in multicellular organisms, like those in humans, is quiescence (7–11). The latter proposition implies that cells will proliferate only when receiving stimulatory signals to do so; this notion is currently promoted in most textbooks of biology and cancer (15,16).

For over 15 years, we and others have challenged these views both on theoretical and experimental grounds while adopting the following two alternative premises: 1) cancer is a tissue-based disease, akin to development gone awry, and 2) explicitly, the default state of all cells is proliferation with variation and motility (13,14,17–20). Under the TOFT framework, primary cancers arise when the reciprocal interactions between parenchyma

and stroma are disrupted, which leads to altered tissue organization (dysplasia, metaplasia, carcinoma in situ) and when the negative (ie, inhibitory) controlling influences exerted by tissues over cells become weaker in their midst. As a result of these latter events, affected epithelial cells regain their default state and thus proliferate and move. Metastatic tumors would be detected when the primary tumor sheds cells/tissues that successfully colonize in near and/or distant tissues or organs.

Controversial Views on the Role of Cell Proliferation in Carcinogenesis and Metastases

Metastases have been the object of concentrated analysis since the second half of the 19th century because of the introduction of novel concepts and technological advances in the biological sciences (eg, Remak's modern cell theory, Virchow's cellular pathology, and technological refinements of the light microscope). During those early days, the origin of cancers was predicated under a consensus that followed the intellectual leadership of German pathologists who claimed that cancer was a tissue-based disease (21,22). Later on, starting in 1914, an alternative view acquired increased popularity when the highly regarded German biologist Theodor Boveri published his book *The Origin of Malignant Tumors,* in which he categorically claimed that cancer was a cell-based disease (23). Soon after, this notion served as the basis for what became known as SMT (12).

The initial reluctance to accept SMT as an explanation for the pathogenesis of cancer abated toward the middle of last century. Before addressing the consequences of adopting SMT with its reductionist underpinnings, we will briefly call attention to two important contemporaneous historical aspects not given the attention they deserve when examining the pathogenetic narrative of this disease. The first is that, in his book, Boveri unambiguously stated that the default state of all cells is proliferation, meaning that this important cell function is a dominant, constitutive property of all cells (23). And the second, is that, from around 1907 to 1912, a group of American researchers lead by the physiologist Ross G. Harrison introduced tissue culture as an important methodological tool to study biological phenomena at large, including cancer (24). Ever since, the reductionist approach of cell culture has played an important role in the development of a rationale to explain the biology of cancer (16). Under SMT, cancer also became a disease of cell proliferation (7,15,16).

In hindsight, it can be surmised that explanations based on cell/tissue culture models missed the true target of carcinogenesis because they seamlessly allowed for the switching of the consensus that proliferation was a dominant, constitutive property of cells to the antithetical one whereby quiescence was perceived to be, instead, the default of cells in multicellular organisms (24). This latter notion was strengthened in the 1960s by the misrepresentation that the serum supplemented to the "chemically defined" culture medium (salts, sugar, amino acids, vitamins, etc.) contained discrete signals that stimulated the proliferation of cells, ie, "growth factors" (25). The conclusion that quiescence was the default state of multicellular organisms has remained unchallenged for almost a century by users of this powerful technological tool (13).

The concept of "growth factor," originally used as an operational description of the nutritive components necessary for the propagation of bacteria (ie, amino acids, sugar, etc.), became that of a stimulatory "signal" to directly induce cells to proliferate in metazoa. This widespread misconception implied that

the main difference between the world of the living and that of inanimate matter was ignored; indeed, in the latter the default state is inertia, meaning that inanimate bodies are passive (inertia is the tendency of objects to keep moving in a straight line at constant velocity; an external force is required to obtain a change of inertial movement); these objects do nothing by themselves. Living organisms, instead, are constitutively active, ie, they move, they proliferate, they metabolize and produce heat. Counterintuitively, followers of the above-mentioned cell culture pioneers adopted the notion that cells in culture conditions acquired the passivity of inanimate objects. In other words, agency, a central property of the living, was transferred to the will of the person who placed the cells in a dish and grew them (24). Later on in the 20th century, the introduction of the idea of a "program" in biology led to the bizarre situation wherein cells needed to receive "information" or "signals" in order to do something that were inherently endowed to do, ie, to proliferate and to move (24,26).

The notion that proliferation is the default state of all cells was implicit in Charles Darwin's 1859 highly influential book *On the Origin of Species* (27). In Darwin's words, "There is no exception to the rule that every organic being naturally increases at so high a rate, that, if not destroyed, the earth would soon be covered by the progeny of a single pair" (27). With the advent of the molecular biology revolution, triggered during the second half of the 20th century by the description of the structure of the DNA molecule, the bulk of cancer researchers adopted a strict reductionist agenda, whose pragmatic outcome has been that SMT became the hegemonic theory of carcinogenesis and metastases (7,11,16,19,28), and the original Darwinian view was replaced by the reductionist modern synthesis (29).

A Brief Historical Account of Metastases in Experimental Biology

Experimental data collected from the late 1950s up to the early 1970s (prominently by Fidler's group among others who used B16 mouse melanoma cells propagated in culture conditions) unequivocally showed that a suspension of single tumor cells injected into the bloodstream of recipient normal mice was less efficient in generating metastases than emboli of five or more of those same cells (30). This unexpected result was interpreted in terms of enhanced cell survival in the clumps, thus remaining consistent with Boveri's originally proposition that cancer was a cell-based, clonal disease (7). In short, research on metastases, as well as in carcinogenesis at large, was centered on the notion that a single "cancer cell" is endowed with all the properties of the disease (7,16).

A few histo-pathological features of metastases are worth recalling in this narrative. For example, breast cancer metastases in brain, liver, lung, bone, and other organs resemble the histo-architecture of a breast, a feature routinely recognized by pathologists to diagnose the primary source of those metastases. Thus, metastases become the result of the anchoring of parenchymal tumor cells or a mix of parenchymal tumor cells and stromal cells into a permissive niche; in fact, biopsies of brain metastases from breast, lung, kidney, and ovarian cancer patients revealed that these metastases contain stromal cells from the primary tumors (31).

Equally relevant, decades ago, Clyde Dawe's group at the National Cancer Institute showed that during normal development the local stroma determines the phenotype of the epithelium (32). Also, the ability to colonize distant organs is not exclusive to cancer cells; namely, during development and adulthood hemopoietic stem cells relocate by a process akin to

metastasis, and they do so even when injected in subcutaneous loci (33). Moreover, during pregnancy, fetal cells colonize a multitude of maternal organs (34,35). Furthermore, endometriosis, a condition having a similar histological pattern to that of normal endometrial mucosa, has been reported to metastasize to the brain, the lung, the kidney, and the liver (36). Compatible with our claim that cancer is development gone awry, it is now well documented that during the metastatic process, the stroma of an organ in which cancer cells anchor plays an important role in determining whether or not those migrating cells will recapitulate the phenotype of the primary tumor (12,37).

The "Muta-Centric" View of Cancer and Metastases

Under the aegis of the SMT, startling technological advances are being used to explore molecular details thought to affect the development of primary tumors and metastases; they include comparative genomic hybridization (CGH), ultra-deep DNA sequencing, and various -omicses. The data collected so far have failed to resolve the cancer puzzle; objectively, no consistent temporal order of when those alleged causal mutations occur during carcinogenesis has been identified (9,38). Researchers pursuing this reductionist approach argue, nonetheless, that the increasingly diminishing cost of genomic analysis justifies expanding the number of tumors analyzed into the hundreds of thousands and the number of cells within those tumors into the millions (39,40). A US government–backed program aims at sequencing the genome of a million tumors. Sobering comments over the use of these sophisticated technological tools have called attention to the high frequency of false-positive and negative results obtained through this technology (41). Notwithstanding, questions regarding whether there are qualitative differences between normal and cancer cells be they in the primary or in metastatic growths remain unanswered and, if anything, they tend to reaffirm the concept that genotypic anomalies do not anticipate phenotypic properties (41,42).

From the SMT perspective, the acquisition of additional mutations in cells of a primary tumor would drive them to thrive in certain organs more than in others (7,30,43). However, so-called driver mutations specific to metastasis in a particular organ have yet to be documented (44). Moreover, this rationale has yet to explain how genuine tumor metastatic cells carrying no mutations generate metastases (45,46).

Darwinian Natural Selection and Metastases

In the last few years, there has been a tendency, largely unchallenged, to favor the notion that cancer metastases are the outcome of a process akin to Darwinian natural selection. However, the proponents of this notion do not rely on Darwin's original text but on the genocentric and reductionist interpretation of Darwin's theory known as the Modern Synthesis (29). Under this latter rationale, individual cancer cells would become subject to a selective process where, spontaneously or by induction (through treatment), those alleged to be the "fittest" among them would survive and eventually drive carcinogenesis toward the death of the stricken host. Implicit in this description remains the notion that primary cancers are made up of heterogeneous populations of cells, an idea that already appeared in early cancer descriptions by Virchow (47). For instance, Graves and Maley recently wrote:

In 1976 Peter Nowell published a landmark perspective on cancer as an evolutionary process driven by stepwise, somatic cell mutations with sequential, subclonal selection. The implicit parallel was to Darwinian natural selection with cancer equivalent to an asexually reproducing, unicellular, quasi-species. The modern era of cancer biology and genomics has validated the fundamentals of cancer as a complex, Darwinian, adaptive system. (11)

In contrast to this view, Darwin opined, instead, that natural selection was taking place at organismic and population levels of biological organization. The notion that natural selection takes place at intra-organismic levels of biological organization remains speculative. Intra-organismal natural selection is predicated on unwarranted extrapolations from two-dimensional cell culture dynamics to the living multicellular organism (see above). These cell culture models represent reductionist approaches aimed at mimicking the intra-organismal complexity of life. They remain outside the realm of Darwinian evolutionary theory because the notion that selection takes place in tissue culture conditions is the result of an anthropocentric construct whereby cells that once integrated an intact multicellular organism re-acquire and retain autonomy inside glass or plastic containers. Also inferentially, under a comparable approach, each of those cells (in culture) has been uncritically considered as if they were unicellular organisms (bacteria, archea or unicellular eukaryotes). Moreover, it has now been documented that at least 6% of human somatic cells carry different versions of our genomes, making us actual genetic mosaics (48); if an intra-organismal selection process were operating, which among these mutated cells would be selected? Finally, multicellular organisms—now plausibly referred to as holosymbionts, ie, organisms made up of billions of somatic cells (metazoan) living in "cooperation" with microbiomes in the skin, the digestive and other systems of their hosts—add further caveats to a speculative role played by an intra-organismal natural selection process (49).

The Why of Metastases

According to the TOFT, cells move from a primary tumor to near or far destinations: first, because of loosened tissue controls that allow them to express their default state, ie proliferation and motility, and secondly, because those cells have recognized a hostile environment in their midst, that is, in the primary tumor. At the tissue level of organization, a "hostile environment" within the primary tumor plausibly means a lack of nutrients, including oxygen. In turn, this local lack of nutrients would unleash the constitutive capacity of those cells to move in search of an optimal nutritional environment. An argument consistent with this interpretation is the evidence referred to by de Groot et al., who reported that the administration of bevacizumab (Avastin) to glioblastomas with the aim of blocking angiogenesis was unexpectedly followed by a highly infiltrative behavior of cells in tumors in these patients (50).

Local invasion by tumor cells represents a frequent, potentially ominous event in the natural history of carcinogenesis. In this regard, Friedl and Alexander concluded that collective multicellular migration is responsible for this phenomenon, which appears to be qualitatively comparable with what happens during normal development (51). This collective cellular migration requires cell-cell junctions (52). Consistent with this notion,

Aceto et al. found that clusters of circulating tumor cells bound to each other by cell-to-cell junctions are critical mediators of cancer metastases both in experimental models as well as in clinical breast and prostate cancer (53). These clusters are tissue fragments released by the primary tumor and not a product of intravascular aggregation. Altogether, this evidence strengthens the conclusions preliminarily advanced by Zeidman and by Fidler in pioneering efforts in the 1950s and 1970s, respectively, whereby multicellular emboli were the more likely source of successful metastatic events when compared with circulating single cells (30,54). Fidler proposed that the higher metastatic success of clusters was because of enhanced survival of tumor cells within them. In contrast to this cell-centered explanation, recent work revealed that metastases contain stroma from the tissue of origin (31). Thus, the "soil" accompanying the "seed" of the primary tumor provides a primer for metastasis implantation. Additionally, and also compatible with our claim that cancer is development gone awry, it is now well documented that during the metastatic process the stroma of an organ in which cancer cells anchor plays an important role in determining whether or not those migrating emboli will recapitulate the phenotype of the primary tumor (12,37).

Whether the mobile, blood-borne epithelial cells that become anchored in new, permissive, suitable niches proliferate or not would depend on the inhibitory control exerted by either the accompanying stromal cells ("old soil") or stromal cells in the loci that they colonized ("new soil"). If the migrating emboli carry only parenchymal cells, chances may be slimmer for them to proliferate and organize into structures resembling those of the primary tumor in the new grounds where they land (31,51).

Thus, altogether, data collected on the pathogenesis of metastases compellingly favors the explanations posited by TOFT, which confers to the multicellular metastatic niche a central role in this process. It further strengthens the claim that cancer is a tissue-based disease or development gone awry.

Conclusions

After a four-decade effort triggered by the declaration of the War on Cancer, the verdict has been unambiguously rendered both by the very early proponents of such approach (4,28) and by others (41,42). Their collective assessment has been that the aims of that gigantic effort remain unachieved and that the financial and manpower investment has fallen short of expectations. Given the scientific, medical, and social relevance of metastases, it is high time to redress the problem now under a more plausible theoretical and pragmatic perspective. Such a perspective is provided by TOFT (55).

Paget's 1889 characterization of metastases as having two main protagonists ("seed[s] and soil") remains today the most accurate explanation of these pathological entities. Implications of this interpretation plus those proposed by TOFT are that: 1) organs where metastases occur have or generate mechano/physico-chemical conditions favorable to the proliferation of migrating cancer cells/tissues (56); 2) single circulating epithelial cancer cells have limited chances of forming metastases, likely because of the "normalizing" influences of the tissue (or the organ) in which those single cells land; and 3) primary cancers and metastases behave as development gone awry. These conclusions are consistent with claims made when TOFT was originally proposed, whereby deleterious cell properties can be reversed by cell-to-cell interactions happening within morphogenetic units in whole organisms, including of course humans. Last but not least, these conclusions widely open the door to alternative preventive and therapeutic approaches to deal with the local and systemic effects of cancer.

Funding

Notes

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