

Are Times a' Changin' in Carcinogenesis?

For the most part, the introductory sentences in many research articles and reviews attempting to explain carcinogenesis do not deviate much from the following narrative ". . . It is generally acknowledged that gene mutations are at the core of the carcinogenic process. . .". Multiple references usually follow this assertion, aimed at buttressing the role of mutations as the direct cause of so-called sporadic cancers, *i.e.* those responsible for about 95% of human cancers. A bibliographical search of these suggested references perpetuate the introductory statement with equally axiomatic assurances. This routine has been exercised for over four decades now, and we suspect that comparable statements will still be printed long after the publication of this current commentary. However, it seems as though new ideas that challenge the main underlying premise of the somatic mutation theory (SMT) are emerging. For the most part, they have asked the following questions: Which are these mutations? How consistently has their appearance been responsible for cancers? When do they take place, and how are they related to the conversion of previously normal tissues to cancerous ones? Unequivocal answers to these sensible inquiries have not been readily forthcoming (1). In fact, increasing numbers of skeptics are voicing their doubts about the value of the SMT (2–6).

Two main forces fuel this revisionist process: the first and more obvious is that, despite the aggressive effort by laboratories around the world to vindicate the SMT and its ancient and modern variations (aneuploidy, oncogene/repressor gene balance, *etc.*), the bill of goods promised after the dawn of the molecular biology revolution has not been delivered (1, 7). The second force is the increasing accumulation of data emphasizing the role of tissue interactions in carcinogenesis (8–10). This almost imperceptible switch of targets from a cell- to a tissue-based etiopathogenesis does not fit easily into the expectations anticipated by the SMT.

Little by little, for the last two decades, pragmatic tissue-based models have been incorporated into the mix of options to explain both carcinogenesis and metastasis. At times tacitly (11), at other times overtly (12), the preeminence of the oncogene/repressor gene theme (the latest incarnation of the SMT) in explaining carcinogenesis has been challenged on a variety of accounts (2). However, most of these tissue-related concepts were introduced using the narrative of a course correction to the prevalent SMT rather than an overt rejection. In addition to mutations, the final outcome in the cancer phenotype had to accommodate the role of stroma-epithelial tissue interactions. An increasing number of researchers are currently favoring this hybrid theory of carcinogenesis that

incorporates elements of the original SMT ("mutations are the cause of cancer") and a role of stroma/epithelial interactions on this process ("context counts") (13). The latter has also been dubbed the epigenetic theory of carcinogenesis, implying that tissue-based phenomena are due to epigenetic gene expression modifications.

In the last few years, theoretical alternatives to the SMT have been postulated, suggesting that carcinogenesis should be considered a problem akin to normal histogenesis and tissue repair, involving the three-dimensional organization of tissues (10, 14). Equally important to this novel approach has been the notion that *proliferation* is the default state of all cells (15, 16). This notion is diametrically opposed to the premise adopted by those who favor the SMT that *quiescence* is the default state of cells in multicellular organisms. This alternative theory incorporating tissues as the target of carcinogens and proliferation as the default state of all cells has coalesced under the name of tissue organization field theory of carcinogenesis and metastasis (TOFT).

Now, in this issue, Barclay *et al.* (17) provide compelling evidence in favor of the TOFT. According to the experimental protocol, it is largely the stroma component of the stroma/epithelial couple, which is responsible for the neoplastic phenotype. Objectively, tissue recombinants involving human prostate cancer-derived fibroblasts and a normal human prostate epithelium cell line derived from a benign prostate hypertrophy (BPH-1) specimen develop as invasive carcinomas when grafted under the kidney capsule of immunocompromised, nude mice. In contrast, recombination of normal stroma or benign prostate hyperplasia stroma with the same epithelial cells does not generate a cancer phenotype. This strengthens the argument that carcinogenesis as well as metastasis is generated by influences of a "modified" stroma over epithelial cells regardless of whether they showed a normal or a cancer phenotype as defined by observations gathered through a light microscope. Also, observations by Barclay *et al.* suggest that the cancer phenotype is reversible provided that the intervening stroma belonged to "normal" or benign prostate hypertrophy sources.

Of course, supporters of the SMT may still argue that the fibroblasts in the stroma of cancers may have accumulated mutations that affect the normal functions of these cells and, consequently, normal epithelial cells would be influenced by the mutated stroma cells and behave in a pattern comparable to that of the genuine cancer epithelial cells (5). As mentioned above, for over four decades, the search for those single or multiple somatic mutations in the epithelial cell that would eventually become endowed with the cancer phenotype has remained elusive. The historical record highlights the fact that, regardless of their worthiness, established paradigms are seldom easily replaced. This is due in part to intellectual inertia and, in this particular case, because of powerful methodologies available to study this most stable of molecules, DNA, in which mutations are supposed to take place. Hence,

Abbreviations: SMT, Somatic mutation theory; TOFT, tissue organization field theory of carcinogenesis and metastasis.

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the search for those mutations may resume in this complex population of stroma cells in yet another *ad hoc* alternative before discarding the SMT. Let us hope that this option will not delay the alternative: to address carcinogenesis and metastasis in a way comparable to how developmental biologists have addressed the study of histogenesis and organogenesis.

It would still be fair to ask. . . Will the identification of the stroma as the culprit in carcinogenesis and/or metastatic development make it easier to pinpoint how cancer, in this case, prostate cancer, evolves? Stroma, as is the case with many other collective nouns, represents a good number of cellular types (fibroblasts, endothelial cells, smooth muscle cells, macrophages, mast cells, and a number of cells that traverse the territory through the blood and the lymph) in addition to extracellular matrix components. Moreover, dynamic changes take place among the above-listed cellular components and the matrix they secrete. Thus, further research on the role played by the stroma in carcinogenesis will have to expand further to eventually clarify which and how these cellular and extracellular cellular components interact to generate the cancer phenotype. A realistic assessment of our current understanding of the cancer puzzle would have to acknowledge that we are all at the beginning of a long journey to untangle the complex interactions among these protagonists. This can be interpreted as the glass half-empty/half-full metaphor. The half-full, optimistic counterpart of the metaphor is the identification of carcinogenesis as a problem of tissue organization and the central role of the stroma in this process. This is as if the proverbial lamppost has been successfully moved to the place where the keys were lost. The half-empty counterpart is that the variables to be tested are multiple and they probably interact simultaneously. A productive exploration of such a complex subject will need a steady support of adequate resources, a realistic management of the hype that has surrounded the cancer field, and a humble attitude toward the years spent following false leads. By facing the data that this and other equally significant contributions in this field have made, it is now becoming evident how much more complex the task is than was thought not long ago.

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