

Somatic Mutation Theory of Carcinogenesis: Why It Should Be Dropped and Replaced

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The somatic mutation theory of carcinogenesis has been the dominant force driving cancer research during the 20th century. In brief, it proposes that successive DNA mutations in a single cell cause cancer (monoclonality). This theory places carcinogenesis at the cellular and subcellular hierarchical levels of biological complexity. Its basic premises are that (1) cancer is a defect of the control of cell proliferation and (2) the default state of metazoan cells is quiescence. These two premises have recently been contradicted by evidence. Supporters of the theory have dealt with these lacks of fit by incorporating ad hoc explanations similar to the use of epicycles in pre-Copernican astronomy. We propose the adoption of an alternative theory, the tissue organization field theory of carcinogenesis and neoplasia. Its basic premises are that (1) proliferation is the default state of all cells and (2) carcinogenesis and neoplasia are defects of tissue architecture. Carcinogens would act initially by disrupting the normal interactions that take place among cells in the parenchyma and stroma of an organ (the equivalent of the "morphogenetic fields" of developing organisms). Stroma appears as the primary target of carcinogens. Carcinogenesis and neoplasia occur entirely through emergent (supracellular) phenomena. Neoplastic cells may be reprogrammed to behave like "normal" cells within normal tissues. We argue that it is necessary to abandon the somatic mutation theory. Researchers will then become free to adopt alternative reliable premises to build a theory that explains carcinogenesis as another outcome, aberrant as it may be, of biological organization. *Mol. Carcinog.* 29:205–211, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

One can go as far as to claim that the resistance of a scientist to a new theory almost invariably is based on ideological reasons rather than on logical reasons or objections to the evidence on which the theory is based [Mayr E. *The growth of biological thought*. Cambridge: Harvard University Press; 1982. p 835].

A further difficulty for the historian is posed by most scientists' unawareness of their own framework of ideas. They rarely articulate—if they think about it at all—what truths or concepts they accept without question and what others they totally reject [Mayr E. *The growth of biological thought*. Cambridge: Harvard University Press; 1982. p 17].

The average cancer researcher is not guided by any grand theory. He or she rather formulates restricted hypotheses for the next few experiments and tends to go on collecting data without reference to the problem of carcinogenesis [Ponten J. In: Iversen OH, editor. *New frontiers in cancer causation*. Washington, DC: Taylor & Francis; 1992. p 59].

We have arrived at the end of the year 2000, and, if you listen to some, perhaps it is now that we are entering a new century and millennium. Although

admittedly artificial, these conventional milestones have been used as timely opportunities to look at what has been learned and accomplished in diverse areas of knowledge during a decade, a century, a millennium. Based on what it is perceived today, brave analysts try to foretell an elusive future in the inherently unpredictable scientific endeavor. The field of carcinogenesis may surely benefit from a timely critical assessment. However, this useful task is unnecessarily complicated because it is unclear which have been or are, for that matter, the fundamental questions cancer researchers have posed in their quest for knowledge in this field.

As the epigrams at the beginning of this editorial suggest, scientists delving into biology in general and cancer researchers in particular have been reluctant to state what premises they adopt or reject and which hypotheses are they exploring. Thus, it is difficult to evaluate their success or failure. Nevertheless, in a recent, rather candid evaluation, failure by default was hinted at by the authors who concluded: "One day, we imagine that cancer biology and treatment—at present a patchwork

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quilt of cell biology, genetics, histopathology, biochemistry, immunology, and pharmacology—will become a science with a conceptual structure and logical coherence that rivals that of chemistry or physics” [1]. In its aftermath, we offer an alternative view based on the research that we have conducted in the last three decades and on the data published by many groups over the past 100 yr. To facilitate its evaluation, this analysis will clearly state the premises being adopted and those being rejected. One incentive to do this is that, with the help of hindsight, a collective perception by participants and observers is beginning to concede that there has been something fundamentally miscued in the previous approaches taken to understand carcinogenesis. An additional incentive is the shared desideratum of all stakeholders to make a rational and logical science out of cancer research [1].

WHERE IS CANCER RESEARCH COMING FROM?

In 1914, Theodor Boveri asked a fundamental question: If normal cells beget normal cells and neoplastic cells beget neoplastic cells, what causes normal cells to become neoplastic? [2]. Boveri advanced the notion that a neoplastic cell arose from “abnormal mitosis” that caused an uneven distribution of the genetic material in their daughter cells: “The cell of a malignant tumor is accordingly . . . a cell with a definite abnormal chromatin-complex” (p. 115). However, an unequivocal answer to Boveri’s original question has yet to be formulated and accepted.

The road to scientific discovery is not a smooth one [3]. For almost 100 yr, it has been assumed that phenotypic changes were due to mutations in the genetic material (*mutation* is derived from the Latin word for *change*). The usage of the word *mutation* has evolved from early in the previous century. In the first 50 yr, it simply implied a change within the chromatin in the cell nucleus; proteins were then thought to be the genetic material. Today, *mutation* means a change in the DNA sequence. The somatic mutation theory, the current prevalent theory of carcinogenesis, is based on this general assumption. That is, a somatic cell in the adult organism would undergo successive DNA mutations, and these mutations would be responsible for the cancer phenotype [1,4,5].

But was it necessary to invoke genomic (DNA) mutations to explain the different behaviors of normal and neoplastic cells? At the time Boveri proposed a first approximation to the somatic mutation theory, most embryologists thought that the generation of diverse tissues from a zygote entailed a segregation of the genetic material [3]. This meant that a liver cell would carry genes different from those carried by a kidney cell. For over half a century, however, we have known that

all cells in the adult human organism contain the same information, i.e., the DNA in a liver cell is identical to the DNA in a kidney cell of the same individual. However, those liver cells beget liver cells, whereas kidney cells beget kidney cells. The difference between these cell types resides in which individual genes are expressed in each of the cells of those organs, generation after generation.

All the information necessary to generate a whole animal is present in the DNA of each somatic cell [6,7]. This notion, several decades old, is seldom mentioned in the context of carcinogenesis. In the past 3 yr, a reaffirmation of this basic concept was provided by Dolly, the now-famous Scottish sheep, whose genome originally belonged to a cell of the mammary gland of another sheep [8]. And, more recently, the nucleus of an embryonic stem cell grown in culture conditions and transplanted into an enucleated egg developed into a whole, viable, fertile mouse [9]. Interestingly, embryonic stem cells similar to these can produce a deadly tumor when placed in the peritoneal cavity of syngeneic mice [10]. Moreover, the once purported irreversibility of “differentiated” phenotypes has just been dealt another, and one hopes, final, blow. Long-term cultured fibroblast nuclei derived from “aged” bulls that were transplanted into enucleated eggs developed into viable, healthy, apparently fertile cloned offspring [11]. Hence, based on this powerful evidence, one may safely conclude that phenotypic changes at the cellular hierarchical level can be the result of either mutations or switches in the expression of certain genes. In other words, cells may show a neoplastic phenotype in the absence of mutations. The field of stem cells has recently exploded as a result of the new possibilities envisioned by this reinterpretation of old and new data.

WHAT IS OBJECTIONABLE ABOUT THE SOMATIC MUTATION THEORY OF CARCINOGENESIS?

The somatic mutation theory squarely places carcinogenesis at the cellular and subcellular hierarchical levels of complexity. This theory relies on two highly questionable basic assumptions. The first is that the main problem of cancer is a defective control of cell proliferation [1,12,13]. This has become a discredited premise, as it is widely acknowledged that the rate of proliferation of cells in neoplasms is not faster than that of cells in normal tissues. The second assumption of the somatic mutation theory is usually unmentioned, and hence, it has remained unchallenged until recently [14]. The current dogma is that the default state of cells in metazoa is quiescence [1,12]. In other words, cells in metazoa would only proliferate when they are “stimulated” by putative oncogenes, growth factors, or their receptors. This assumption ignores the fact that proliferation is the acknowl-

edged default state of procaryotes, unicellular eucaryotes, and plant cells [12,14]. Proponents of quiescence as the default state of cells in metazoa have yet to offer a reasonable explanation for such a radical evolutionary discontinuity. The Darwinian principle of common descent instead favors maintaining proliferation as the default state for metazoa. As remarked by Dobzhansky several decades ago, all biological phenomena would have to make sense in the context of evolutionary theory, and this should include carcinogenesis.

The somatic mutation theory is fraught with additional inconsistencies. For instance, it fails to adequately address the subject of proliferative autonomy by cells forming a tumor. The proliferation rate of cells in neoplasms of hormone-target organs, such as those in breast and prostate carcinomas in humans and their equivalents in rodents, is susceptible to the hormonal milieu in the host. At least for a while (a long while in many cases), breast and prostate neoplasms regress when their trophic hormones are removed [15]. These hormone-regulated proliferative patterns imply that tumor cells are not inherently autonomous entities. In addition, metastatic tumors may remain silent for years [16].

Returning to the desirable evolutionary outlook when framing a theory of carcinogenesis, the somatic mutation theory even becomes counter-intuitive. Researchers consistently, and very efficiently one may add, generate neoplasias by subjecting experimental animals to a variety of physical, chemical, or biological carcinogens [for pertinent reviews, see 17–19]. The central tenet of the theory is that, after these deleterious treatments, successive DNA mutations in a single cell will transform it into a neoplastic cell. The notion of monoclonality in tumors is based on this assumption. A plausible explanation should be advanced to justify how such an abused cell would curiously become endowed with the permanent condition of proliferating autonomously at a rate higher than that of cells not subjected to the mutational damage.

Ad hoc explanations were raised to reconcile these contradictions [20]. Even commentators who have adopted the somatic mutation theory as their strategic blueprint have characterized as “astounding” some of the conclusions drawn from projections on how many mutations are involved in generating a cancer phenotype [21]. These figures have varied wildly, from just three [22] to anywhere from 11 000 [23] to 100 000 [24] mutations. To compound these contradictions, the time frames under which some of the crucial mutations occur do not fit claims about their alleged causal significance. For instance, comparable genomic instability indices have been found in both benign and malignant lesions in the colon [25]. In addition, a “mutator” phenotype was proposed to explain the

number of mutations found in neoplasms [4,26]. A candidate target for the establishment of the “mutator” phenotype has been the *p53* gene, the proclaimed “guardian of the genome.” A disabled *p53* gene would allow for an increased rate of genomic mutations and rearrangements. However, *p53* gene mutations appear to be acquired by cancer cells at a time when the carcinogenesis process has been already well underway [21,27].

Lack of fit stemming from the adoption of the somatic mutation theory of carcinogenesis has been dealt with by supporters of the theory in a manner comparable to those adopted by pre-Copernican astronomers who dealt with the lack of fit between theory and data on the motion of the planets. They added ever-increasing numbers of epicycles to the planets’ orbits. The resolution of those inconsistencies was to remove the Earth from the center of what was the Ptolemaic universe and place the Sun there instead [28]. We suggest that this metaphor is valid for carcinogenesis today.

CARCINOGENESIS AS VIEWED BY PATHOLOGISTS AND DEVELOPMENTAL BIOLOGISTS

Since the 19th century, pathologists have described the histologic pattern of tumors with the light microscope. What they saw was an altered pattern of tissue organization. They still do. This is clearly stated in current pathology textbooks and treatises [29–31]. Nevertheless, in the second half of the 20th century, pathologists wondered whether a fundamental change in how cancer was diagnosed was about to materialize in the immediate future. A telling example of this tendency appeared in the third edition (1967) of the popular Robbins’ *Pathology* textbook: “It is quite remarkable that in a day when man is on the threshold of mastering outer space, the diagnosis of cancer still rests principally on the subjective impression of the pathologist” (p. 105) [32]. This statement stealthily implied that, at the core of carcinogenesis and neoplasia, there must have been a simpler, more satisfying, “molecular” explanation. The expectation that molecular probes would replace the light microscope in making the diagnosis of tumors has yet to materialize.

Alternatively, research contributions originating at the interface between developmental biology and cancer have provided a significantly different explanation of carcinogenesis. Only a few will be highlighted in this essay [for an expanded treatment of the subject, see 14]. In the 1960s and 1970s, it was observed that, in teratocarcinomas, the stem cells not only generated more stem cells but also “differentiated” cells that gave rise to nontumorigenic tissue. These findings challenged a fundamental assumption of the somatic mutation theory, i.e., “once a cancer cell, always a cancer cell” [33]. Epigenetic mechanisms were considered to be at

work. The teratocarcinoma cells were generated from tumors resulting from the implantation of normal embryos into ectopic locations. Subsequently, teratocarcinoma cells injected into normal blastocysts were shown to generate normal tissues (including gonads) in viable mosaic individuals resulting from this manipulation [34,35]. In subsequent generations, normal offspring resulted from the genome of a cell that was once a cancer cell. If cancer indeed results from the accumulation of DNA mutations in a previously normal cell, it becomes problematic to explain these data. Specifically, the causal role of somatic mutations on carcinogenesis becomes substantially undermined, if not practically “falsified.”

A REVISIONIST VIEW OF CARCINOGENESIS: THE TISSUE ORGANIZATION FIELD THEORY

Many researchers working within the premises adopted by the somatic mutation theory of carcinogenesis may reluctantly acknowledge that they are far from reaching the eventual vindication of this theory. However, in their view, these shortcomings will be remedied by accumulating more data. This misperception contributes to the adoption of a conservative attitude whereby data are constantly generated, producing in turn ever-increasing glaring inconsistencies.

Thus, if a plausible alternative does exist, on what premises is it grounded? Is the course correction to be made a minor one, or is it of a significant magnitude? Our analysis of the data collected by others and ourselves has led us to propose the adoption of two fundamental premises on which to base a theory of carcinogenesis. The first one states that proliferation is the default state of all cells. Above and elsewhere we have referred to the

epistemological bases for adopting this premise [14]. The felicitous metaphor proposed by François Jacob, that Nature is a tinkerer and not an engineer, underlies the notion that cells in increasingly complex settings maintain strategies that were successfully tried in simpler models and acquire new ones when in contact with their peers, forming a tissue (emergence).

The second premise is that carcinogenesis and neoplasia are defects of tissue architecture. Specifically, the targets of carcinogens would be all the morphogenetic fields comprising interacting tissues. In this context, physical, chemical, and biological carcinogens qualify as disruptors of tissue architecture. Now, let us look at the evidence. Histogenesis occurs during embryonic and fetal development as an orderly process regulated by cell-to-cell interactions within “morphogenetic fields” [36]. These fields retain their functional integrity throughout the life of the individual. However, their ability to successfully regenerate or repair tissue damage differs across species and diminishes with age. In short, we propose that neoplasias are emergent phenomena resulting from a flawed interaction among cells and tissues (Table 1). We called this alternative theory the tissue organization field theory of carcinogenesis and neoplasia [14].

Carcinogens would act initially by disrupting the normal interactions that take place among cells in the stroma and parenchyma of an organ (the equivalent of the “morphogenetic field”). This disruption would result in a lessening of the cells’ ability to “read” their positional and historical background. An initial alteration of the stroma–epithelium interaction would be a hyperplastic state. Next, the tissue organizational pattern

Table 1. Comparison of Competing Theories of Carcinogenesis

Somatic mutation theory	
Premises	
	Default state for cells in metazoa is quiescence
	Control of the cell cycle is equivalent to the control of cell proliferation
	Carcinogenesis takes place at the cellular or subcellular hierarchical level of complexity
	Neoplasias are monoclonal
	Neoplasias arise when genes involved in the control of the cell number are mutated
Mechanisms	
	Altered growth factor signaling pathways
	Altered cell-cycle effectors (cellular oncogenes, cyclins, etc.)
	Ad hoc additions: altered inhibitory factors and suppressor genes, regulation of cell death, and differentiation pathways
Tissue organization field theory	
Premises	
	Default state for all cells is proliferation
	Carcinogenesis takes place at the tissue hierarchical level of complexity
Mechanisms	
	Altered cell-to-cell interactions
	Altered tissue-to-tissue interactions

becomes altered (dysplasia) or even adopts a different tissue type (metaplasia). The pattern of progression to carcinoma *in situ* may not necessarily follow this sequence [37]. If the carcinogen action persists, eventually a full neoplastic state evolves. These stages can be reversed if no new damage is sustained. According to this theory, the effects of carcinogens on intracellular structures and organelles (including genomic mutations), although variably deleterious to all of them, are not directly responsible for the development of a neoplasia.

ADDITIONAL SUPPORTING DATA

The notion that carcinogenesis and neoplasia occur entirely through emergent (supracellular) phenomena had been advanced by Orr and Spencer [38,39] in England from the 1940s to the 1960s. Their experiments involving chemical carcinogenesis of the skin by local application of 20-methylcholantrene or 7,12-dimethylbenz[*a*]anthracene suggested that the stroma, not the epithelium, is the primary target of the carcinogen. Ever since, additional contributions to the notion that stroma or epithelium disruption is responsible for carcinogenesis have been published [40–45]. More recently, ectopic expression of stromelysin-1 by mammary gland epithelial cells in transgenic animals resulted in mammary gland carcinoma. In this case, the expression of this enzyme induces stromal changes that in turn would lead to carcinoma. Treatment with specific protease inhibitors blocked carcinogenesis in this model [46]. Also, irradiation of the stroma of epithelium-free mammary glands results in carcinogenesis in nonirradiated mammary epithelial cells inoculated into the irradiated stroma [47]. In all these experiments, the stroma seem to be the primary target of the carcinogen.

Researchers siding with the somatic mutation theory may be tempted to offer another epicyclical argument whereby the carcinogen may have mutated the stroma cells. In this context, however, mutations cease to be a good explanation for how an epithelial cancer cell differs from a normal epithelial cell that begot the neoplastic cell. To summarize, whereas the somatic mutation theory places the target of carcinogenesis at the subcellular level of biological complexity (mutations of genes involved in cell-cycle control and signal transduction), the tissue organization field theory posits that the target of carcinogens is tissue organization (cell-cell and cell–extracellular matrix interactions).

From the perspective of the tissue organization field theory, neoplastic cells may be reprogrammed to behave like “normal” cells within normal tissues. Since the 1960s, this notion has been vindicated with a variety of experimental models, all of them showing that malignancy can be manipulated into normalcy. For instance, neoplastic rat liver cells

injected into the liver become part of normal rat hepatic parenchyma [48]. Manipulation of the extracellular matrix also results in the suppression of the cancer phenotype [45]. It should be stressed, however, that these data are not directly linked to the subject of carcinogenesis *per se*. Rather, these experiments underlie the susceptibility of already neoplastic cells to become “normalized” by a “normal” microenvironment. These experiments also undermine the long-held notion that mutations are responsible for the cancer phenotype.

THE COMMONALITY BETWEEN TERATOLOGY AND CARCINOGENESIS

The tissue organization field theory views teratology and carcinogenesis as two related processes in which the tissue architecture is disrupted. Whereas teratogens disrupt embryonic or fetal development, carcinogens act across all phases of development, including the *in ovo* and *in utero* stages plus those of infancy, puberty, adulthood, and old age. From this perspective, carcinogens need not be mutagens [14].

The tissue organization field theory of carcinogenesis also accommodates the fact that an increased incidence of somatic mutations in cells may take place during carcinogenesis and neoplasia. Although a legitimate subject of inquiry in its own right, these mutations represent epiphenomena unrelated to cancer causality [14,46].

SUMMARY

The zeitgeist of the past 50 yr has been that the answer to most biological questions was inevitably found at the lowest level of hierarchical complexity. This approach has been extremely productive when this strategy was applied to phenomena that *a posteriori* were found to occur at that lower level of complexity. One example of this success is sickle cell anemia, where the properties of the mutated hemoglobin molecule adequately explain the signs and symptoms of the disease (the phenotype). Conversely, the equally well-characterized mutations that “cause” the metabolic Lesh–Nyhan syndrome (attributed to a mutation in the hypoxanthine phosphoribosyltransferase gene) and the neuroblastomas in the *lgl-2* *Drosophila* mutants have not shed light on the respective resulting phenotypes because the respective mutated proteins are indirectly responsible for the phenotypes.

It is commonly stated that the somatic mutation theory addresses carcinogenesis in a mechanistic perspective, whereas alternative hypotheses do not. It is time to take these pronouncements at face value. The factual record shows that the concerted effort of a century of research based on the somatic mutation theory falls short of providing either a “mechanistic” or any other evolutionarily relevant explanation for carcinogenesis.

Rather, if carcinogenesis is acknowledged to be a tissue-based emergent process, as posited by the tissue organization field theory, the most promising strategy should be that used by developmental biologists and geneticists in their quest to understand histogenesis and organogenesis. Investments on this approach have already illuminated these research areas. Indeed, developmental biologists have identified genes, the proteins they code, and the extracellular ligands they interact with at the appropriate level of complexity, i.e., when and where they matter for histogenesis.

Peyton Rous was correct four decades ago when he said that the somatic mutation theory "acts like a tranquilizer" on the creativity of researchers in this field [49]. Only when this theory is abandoned will researchers become free to adopt alternative reliable premises to build a theory that explains carcinogenesis as an outcome of biological organization. Otherwise, new epicycles will be added to a theory already brimming with ad hoc explanations.

The available alternatives are thus few and clear: (1) to keep consuming the tranquilizer provided by the somatic mutation theory, (2) to adopt the tissue organization field theory, or (3) to find a worthy option to alternatives 1 and 2. Looking at carcinogenesis from an optimistic perspective, interesting times are just ahead in the upcoming decade, century, millennium!

NOTE ADDED IN PROOF

In a recent opinion piece, Folkman et al. (Nature Reviews Molecular Cell Biology 1:76–79, 2000) also highlight the glaring inconsistencies of the data collected under the somatic mutation theory. They propose that in addition to the "gene-centric" approach, researchers adopt a complementary one in which "epigenetic, cell-cell, and extracellular interactions are also pivotal in tumor progression."

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