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THEORIES of CARCINOGENESIS: An Emerging Perspective

Carlos Sonnenschein and **Ana M. Soto**
Tufts University School of Medicine, Department of Anatomy and Cellular Biology, 136 Harrison Ave, Boston MA 02111

Abstract

Four decades ago Leslie Foulds remarked that "Experimental analysis has produced an alarming mass of empirical facts without providing an adequate language for their communication or effective concepts for their synthesis." Examining the relevance of the data avalanche we all generate and are subjected to in the context of the premises and predictions of the current cancer theories may help resolve this paradox. This goal is becoming increasingly relevant given the looming attempts to rigorously model and parameterize crucial events in carcinogenesis (microenvironmental conditions, cellular proliferation and motility), which will require the adoption of reliable premises on which to base those efforts. This choice must be made *a priori*, as premises are not testable, and data are not free of the theoretical frame used to gather them. In this review we provide a critical analysis of the two main currents in cancer research, one centered at the cellular level of biological organization, the somatic mutation theory, which conceptualizes carcinogenesis as a problem of cell proliferation control, and the other centered at the tissue level, the tissue organization filed theory, which considers carcinogenesis a process akin to organogenesis gone awry.

Keywords

microenvironment; stroma; proliferation; stroma-epithelium interactions; tissue organization field theory

Carcinogenesis continues to be a highly controversial subject despite the incessant stream of publications aimed at explaining it. It would be sensible to find an answer to this paradox, i.e., increased accumulation of data and no commensurate clarification of this important biomedical problem. Examining the relevance of the data avalanche in the context of the premises and predictions of the current cancer theories may help resolve this paradox. This goal is becoming increasingly relevant given the looming attempts to rigorously model and parameterize crucial events in carcinogenesis (microenvironmental conditions, cellular proliferation and motility), which will require the adoption of reliable premises on which to base those efforts [1]; and in this issue).

To avoid unnecessary confusions regarding the theories of carcinogenesis and the premises that underlie them, it will be useful to identify the different types of human cancers that exist. First, there are those that are inherited through the germline of the carriers; they represent about 5% of the total incidence of human cancers. There is consensus about the mutational origin of

Corresponding Authors: Carlos Sonnenschein MD/ Ana M. Soto MD, Phone: 617 636 2451/ 617 636 6954, Fax: 617 636 3971, Emails: carlos.sonnenschein@tufts.edu/ ana.soto@tufts.edu.

these inherited cancers. And then there are those called “sporadic” that represent 95% of all clinical cancers and are caused by a variety of widely differing carcinogens present in the environment (chemical, physical and biological agents). In order to explain the development of sporadic cancers two main theories have been proposed and a third is increasingly gaining adepts (see below). Given their clinical importance and the magnitude of their incidence, our analysis will mainly concentrate on explanations on how known causative agents generate the sporadic variety of cancers.

Theories of carcinogenesis

The *somatic mutation theory* (SMT) has been the prevailing one in cancer research for the last 50 years [2]. It is based on the following premises: 1) cancer is derived from a single somatic cell that successively has accumulated multiple DNA mutations (monoclonality), 2) those mutations occur on genes that control cell proliferation and the cell cycle [3] and 3) implicitly, the default state of cell proliferation in metazoa is *quiescence*. In 1999, based on our work on the control of cell proliferation and a comprehensive analysis of the literature, we proposed an alternative theory, the *tissue organization field theory* (TOFT). Its premises are significantly different from those of the SMT, namely, 1) carcinogenesis is a problem of tissue organization, comparable to organogenesis during early development, and 2) *proliferation* is the default state of all cells [4,5]. Each of these premises has precedents made by the German School of Pathology in the last decades of the 19th century [6,7]. Finally, there are hybrid theories resulting from the lack of fit between the predictions of the SMT and the increasing number of experimental observations that cannot be accommodated within a cell-centered approach to carcinogenesis. This option melds the SMT with the concept that cancer is also due to anomalies in tissue organization [8-11]. Undoubtedly, only time will provide the necessary, decisive perspective to validate which of these theories most closely explains carcinogenesis [12]. Meanwhile, we will compare the above-referred competing views from today's perspective, but before doing this we will briefly elaborate on the premise of the default state of cells since it represents the sharpest difference among the three theories on the subject.

The default state of cells in metazoa

Among microbiologists, it is axiomatic to accept that *proliferation* is the default state of prokaryotes and unicellular eukaryotes [13]. It is therefore puzzling to note that the majority of researchers delving on metazoan biology have ignored whether or not the default state of cells in metazoa was a relevant premise to consider in this context. The nature of the default state is not only an important theoretical issue; it has also heuristic implications. When planning experiments, researchers implicitly or explicitly decide which premises to choose. The adoption of one of these two alternative views determines the type of experimental program that will be conducted, and hence, it is at the core of the research program of the competing theories of carcinogenesis [14-16].

Based on an evolutionary perspective and on our experience using a variety of cell culture models and their animal counterparts, we favor the concept that the default state of cells in metazoa, like those of unicellular organisms and metaphyta, is *proliferation*. In a recent revisiting of the subject, we became aware that at the end of the 19th century, the famed pathologist H. Ribbert postulated that cancer cells, freed from the restraint of tissue structure, would express their constitutive property to proliferate [6]. Ribbert's view was foreshadowed by Weigert (1882) and Roux (1888)[7]. Thus, even though there is a long dating precedent for the view that proliferation is the default state of cells, for near a century this principle has been practically ignored both in textbooks and by experimentalists when discussing either the control of cell proliferation or carcinogenesis. As a result, the premise that *proliferation* is the default

state of all cells failed to be incorporated among the basic tenets of experimental biology [17, 18].

We and a few others have addressed the subject while using estrogen target cells [19-21]; still others showed that the quiescence of lymphocytes is actively maintained (i.e., it is induced) [22,23], and that this proliferative quiescence was not just a consequence of the expression of a cellular differentiation program, as recently suggested [18,24].

About “causes” and “explanations” in cancer

The lack of precision in the use of the words “cause” and “explanation” has been a source of confusion in the field of carcinogenesis. More to the point, there is general agreement about which external agents cause cancer. These “cancer agents” can be neutralized either by preventing exposure (reducing or abolishing tobacco smoking, providing asbestos-free environments, etc) or by treatment of the condition to which the cancer process has been linked [antibiotics for bacterial [25] or parasitic infections [26], antibodies in the form of vaccines for viral infections [27] (Figure 1). In any case, it is clear that the above-referred interventions are not “cancer cures.”

There are competing interpretations, however, about how to link these diverse agents to an explanation of why and how the cancer phenotype arises. To this end, we will compare and contrast the SMT, which is cell-based, and the TOFT, which is tissue-based. There are various theories straddling these two levels [28,29]; however, they will not be discussed here as the issue we are addressing does not require their analysis.

Proponents of the SMT claim that those widely dissimilar agents would somehow cause either the propagation of already mutated cells or generate mutations in genes that either directly or indirectly mediate the control of the proliferation of cells that would eventually become neoplastic. Hence, the cause of cancer would be DNA mutations, and the explanation of the cancer phenotype becomes altered control of cell proliferation, or of the cell cycle. From this perspective, both the cancer cause and its explanation reside at the subcellular and cellular levels of biological organization (Figure 1).

Alternatively, the TOFT proposes that carcinogenic agents generate a disruption in the reciprocal interactions between cells that maintain tissue organization, tissue repair and local homeostasis. In these altered microenvironments, the negative controls exerted by tissue organization are relaxed; hence, the parenchymal cells would be allowed to exercise their constitutive ability to proliferate and migrate. The explanation of the cancer phenotype offered by the TOFT is that these alterations generate an abnormal tissue architecture that would deviate from normalcy as the tissue homeostasis becomes increasingly disrupted. From the TOFT perspective, both the cancer cause and its explanation reside at the tissue level of biological organization (Figure 1).

In a brief reference to the hereditary tumors, both the SMT and the TOFT share the notion that they are *caused* by germplasm DNA mutations. However, while the SMT seeks to explain how these mutations alter the proliferation of the cells that express the mutated gene, the TOFT seeks to explain how these mutated genes would generate an altered histogenesis and organogenesis. In the context of the TOFT, the mutated gene would code for a protein(s) that would play important roles in regulating the normal formation of morphogenetic fields in which those tumors appear. For this reason, we have called these tumors “inborn errors of development”. The prototypic example of this type of neoplasm is the *lethal giant larva 2 (lgl2)* tumor in Drosophila [30]. In humans, these types of tumors include retinoblastomas, Wilms' tumors, the BRCA1 and 2-linked breast and ovarian tumors and a few others.

Another significant subject in this panoply of issues related to carcinogenesis is the one dealing with tumor susceptibility [31]. We will not address this issue at this time.

An update on the Somatic Mutation Theory

The main driving force of the SMT program has been its reductionist core. In this tradition, it is assumed that organismic phenomena can be advantageously reduced to cellular and/or subcellular ones. Thus, when reducing cancer to a cellular phenomenon, neoplasms become *de facto* reduced to a single transformed cell and carcinogenesis becomes equivalent to enhanced proliferation of cells in a dish. Most of this research has been, and is still, conducted using 2-dimensional *in vitro* models, where primary cell cultures and established cell lines are the representative tools. From this seductive simplicity, whereby a single or a few oncogene (s) may induce cancer, an increasingly complicated picture has mushroomed into more than 350 oncogenes and tumor suppressor genes identified as putative *causes* of cancer… and these numbers are predicted to increase [2]. However, if oncogenes were indeed dominant determinants, as originally claimed, the need for additional gain-of-function effects attributed to these mutated genes would appear as redundant and difficult to rationalize [32]. To accommodate these inconsistencies that would have led to invalidate the SMT, an *ad hoc* alternative was proposed whereby oncogenes, in addition to disrupting the proliferation control of the cells that harbor them would exercise their effects indirectly by affecting tissue organization [8,33].

Accommodating *ad hoc* arguments have also surfaced regarding the unfulfilled prediction of a higher mutation rate and consequent increased cancer incidence due to a mismatch repair (MMR) deficiency [34]. Kinzler & Vogelstein pondered about this paradox and concluded: “Why isn't MMR deficiency as carcinogenic as mutagen exposure? One possibility would be that mutagens are carcinogenic not only because they induce mutations, but also because they cause substantial cellular death with consequent tissue regeneration.” And, “Thus, it is possible that the dietary factors which lead to colorectal cancer are not mutagens, but rather irritants that lead to tissue regeneration.” [35]. Clearly, these explanations highlight processes that take place at the tissue level of organization such as injury and inflammation, which are central to the explanation of carcinogenesis by the TOFT. Hence, this rationalization represents another example of the recent tendency of hybridizing the SMT and the microenvironmental origin of neoplasias.

A recent addition to the variants of the SMT has been called the *clonal genetic model of cancer* [36]. Despite acknowledging the above-mentioned objections to the classical view of the SMT, mutations in oncogenes and suppressor genes are central to this theoretical variant. An epigenetic component is here added to those stable genetic mutations which include “global DNA hypomethylation, hypermethylation and hypomethylation of specific genes, chromatin alterations and loss of imprinting” which could all “lead to aberrant activation of growth-promoting genes and aberrant silencing of tumor-suppressor genes.” As in other theoretical alternatives aimed at overcoming the inadequacy of the original SMT, genetic and “epigenetic”[1] changes are mixed and matched following an unpredictable pattern that has to accommodate increasingly complex experimental or clinical lacks of fit.

As we argue below, carcinogenesis and metastases can be considered as initially limited tissue-based phenomena. Thus, cellular-based (gene mutations, chromosomal atypias, carbohydrate metabolism anomalies, nuclear size and shape peculiarities, etc) like organismal-based

[1]Here, the word epigenetic is narrowly interpreted as changes limited to subcellular alterations of DNA methylation, histone modification, chromosome structure, loss of imprinting and their combinations.

manifestations (pain, cachexia, tumors and finally, death) are the consequences of cancer, and, not its cause.

Still another alternative to the classic SMT has been proposed under the ubiquitous use of the stem cell concept. This option implies that cancers would appear as a result of gene mutations on operationally-defined, elusive individual stem cells. This theoretical variant proposes that the original clonal, mutated cells have innate "immortal" properties [37]. It remains unclear in what way "stem cells" as putative originators of neoplasms represent either a conceptual or a pragmatic improvement over the shortcomings of the SMT. In other words, how would a stem cell-based alternative overcome the criticisms over a cell-centered theory when compared to any other cell type that populate multicellular organisms.

An update on the Tissue Organization Field Theory

The TOFT predicts that neoplastic phenotypes are potentially reversible through cell-cell and/or tissue-tissue interactions. This has been verified experimentally [38-40]. A now classical example is the normalization of teratocarcinoma cells injected into blastocysts [41]. Moreover, nuclei from a variety of cancer cells transplanted into enucleated oocytes could support normal pre- and post-implantation development [42,43]. Also, modification of extracellular matrix components resulted in normalization of the neoplastic phenotype [44-46].

The ability of normal tissues to reverse the neoplastic phenotype is subject to the age and physiologic status of the host. For instance, mammary gland stroma from mature and multiparous rats prevented neoplastic development and resulted, instead, in normal ductal growth of grafted epithelial cancer cells [47]. This tumor development pattern suggests a parallel to the phenomenon of age- and parity-dependent susceptibility and resistance to chemical carcinogens in mammary gland neoplasia. As susceptibility to carcinogenesis decreased with age, the ability of the stroma to normalize neoplastic epithelial cells increased. This tissue-mediated, age-dependent normalization showed an inverted age-dependent pattern when rat liver carcinoma cells were tested [48]. In addition, human metastatic melanoma cells injected into zebra fish embryos acquired a non-neoplastic phenotype, while they formed tumors when injected into zebrafish once organogenesis was completed [46]. Altogether, these experiments suggest that the cancer phenotype is an adaptive, emergent phenomenon taking place at the tissue level of organization.

Experiments designed under a theory-neutral strategy showed that the tissue recombination of mammary gland stroma exposed to a carcinogen with unexposed, normal mammary epithelial cells resulted in adenocarcinomas. However, the reverse combination did not [49]. This observation suggests that the stroma, rather than the epithelium, was the target of the carcinogen [50] and challenges the notion that carcinogens cause mammary gland adenocarcinomas by mutating the DNA of the epithelial cells.

In sum, alterations in tissue architecture can and do induce neoplasms, and those neoplasms, like the sporadic ones in humans, may end up showing aneuploidy [51] and even mutations [10]. But, as Prehn remarked, "it may be more correct to say that cancers beget mutations than it is to say that mutations beget cancers." [52]. Nevertheless, some have recently proposed to switch the focus of investigation to the search for hypothetical cancer-causing mutations now in stromal cells [39,53]. It remains unclear how this alternative would overcome the shortcomings of the SMT [54].

Would it be productive to reconcile the SMT and the TOFT?

Metaphors and images have been used in order to shed light on the subject of explaining cancer. The SMT centers on "one renegade cell," and views cancer as a cell-based disease involving

unregulated cell proliferation [55]. The TOFT, instead, focuses on a "society of cells" and views cancer as a problem of tissue organization [39]. Hence, as hinted above, explanations of the process of carcinogenesis by these two theories belong to distinct levels of biological complexity and, therefore, are incompatible, as are their philosophical stances (reductionism versus organicism, see below).

The above-referred incompatibilities do not rule out, however, that the data gathered from experiments based on the SMT might be interpreted either in the context of the TOFT, or even to refute the arguments of the SMT. For instance, the polyps in humans hemizygous for a defective adenomatous polyposis coli (APC) gene, the dysplasias appearing prior to neoplasia in retinoblastoma, the *lethal giant larva* mutant in Drosophila and the other conditions briefly referred to above are all anomalies of normal tissue organization. In the case of inactivated APC, one may even suggest an explanation, since the APC protein binds to β-catenin, which in turn binds to cell adhesion molecules (cadherins) [56]. APC also binds to the human homologue of Drosophila *discs large* (hDdl), which is also involved in cell-to-cell adhesion through septate junctions [57]. Deletions of this gene result in the loosening of cell-cell contacts, abnormal morphology of the imaginal discs, and neoplastic development [58]. From the TOFT perspective, one would study how alterations in APC, catenins, cadherins and hDdl affect the development of the intestinal crypt and give rise to polyps. Instead, the SMT-based research effort centers on the role of β-catenin as a transcription factor and looks at the transcriptional machinery in the epithelial cell nucleus in search of alleged alterations on the control of cell proliferation, the cell cycle and/or apoptosis. In fact, evidence collected while using the human APC mutants and the experimental *Min* mouse model suggests, instead, that no alteration in the control of cell proliferation in the intestinal epithelium is apparent; what appears consistently is an alteration in the splitting of the crypts (crypt fission) in the intestines of these carriers, i.e., an altered three-dimensional intestinal tissue-specific malformation that seems to be at the core of adenoma enlargement [59].

In the last decade, as already documented above, a substantial number of scientists have moved from a hard-core SMT stance to acknowledge a decisive role for a tissue component in carcinogenesis. This resulted in a narrative of the carcinogenic process that invokes the role of the 'microenvironment' but is still dominated by a genetic deterministic rhetoric. From this perspective, stromal alterations would result in genomic instability of the epithelial cells [10]. This interpretation entails a causal sequence whereby overexpression of matrix metalloproteinases generates free radicals that would mutate epithelial cells, and these mutated cells will then develop into a cancer. Thus, according to this particular hybrid view, the role of the tissue environment would be to generate reactive chemicals that will mutate the DNA of epithelial cells. However, this attempt to reconcile the two theories does not provide any explanatory advantage over the "classical" SMT.

Recently, another hypothetical contribution aimed at explaining carcinogenesis has been presented whereby the core causal element of the SMT, i.e. somatic mutations, is criticized but not dismissed [53]. In fact, as referred to above, the causal role of mutations on the epithelial cells in the carcinogenic process is now transferred as well to the cellular components of the nearby stroma. This variant of the SMT ("a different two-hit model") does not differ much from those alternatives sharing with all the others the implicit premise that *quiescence* is the default state of cells in metazoa, a notion that lacks evolutionary relevance [16,18].

Additionally, it was proposed that matrix metalloproteinases play a decisive role in carcinogenesis by "activating" growth factors and cell surface receptors and by facilitating paracrine signaling pathways, among other possible routes [60,61]. In this reassessment, cancer would still remain a problem of control of cell proliferation, A stealth implication of this increasingly popular view of melding the SMT with tissue-based theories is that this would

cover all possible outcomes preventing a resolution of the question… how is cancer explained? In other words, no hypothesis would be tested because no hypothesis could be rejected.

Development and carcinogenesis: Taking sides over underlying premises and research programs

As François Jacob noted, nature is not an engineer, but a tinker— a given molecule is put to different uses during evolution [62]. Thirty years after this famous dictum was coined, the concept of signal specificity, central to the original version of the SMT is being challenged because of the massive experimental evidence revealing the multiple interactions of a given protein with other proteins. Early during the molecular biology revolution, the lack of a unique correlation between a given protein and its function was addressed by Hull as the problem of "the many and the many" [63]. In other words, one phenotype could result from several different molecular mechanisms, while a single gene may participate in the generation of multiple, distinct phenotypes. A clear example of this divergence is polyphenism, i.e., a single genotype producing several different phenotypes. That single proteins display multiple activities and a single genotype generates diverse phenotypes argues against reductionist explanations in multicellular organisms.

A couple of examples in the field of developmental biology also point to the difficulties encountered by embracing the notion of specificity for each signal and for each pathway in determining a phenotype. A compelling example stems from studies in mice generated through cloning by nuclear transplantation; these studies showed that altered gene expression involving as many as a staggering 4% of a set of 10,000 genes resulted in a normal phenotype at the cell, tissue and organ levels of complexity [64]. This indicates a significant degree of tolerance of abnormal gene expression compatible with normal development.

Another example relates to the validity of the "instructive" hypothesis of differentiation. Hormones and cytokines are supposed to determine a specific phenotype in target cells by inducing a lineage-specific gene-activation program. The specificity of the response was found not to reside in the hormone, its receptor, or the signal transduction pathway [65]. The specificity of the response appeared to be determined, instead, by an apparently unrelated differentiation process. Again, this observation points to the lack of a unique, exclusive correlation between a given protein and its biological functions. The promise that the specificity of the effect of a given hormone could be understood by the study of interactions between the receptor and the hormone, and the subsequent activation of the transduction pathway downstream, has yet to be fulfilled. Specificity is to be found elsewhere [64].

The limitations of the reductionist, bottom-up approach in dealing with complex biological phenomena, like carcinogenesis, stresses instead the heuristic advantage of searching for explanations at the level of organization at which a phenomenon is observed, while gingerly moving up and down levels of organization to account for bottom-up and top-down causation [15,66].

Conclusions

While providing extremely sophisticated, reliable details of processes happening inside cells, the reductionist, gene-centered strategy of the SMT appears to be irrelevant, however, to the resolution of the cancer puzzle. During the last three decades, the field of cancer research has witnessed a slowly but relentless switch of emphasis in searching of explanations for carcinogenesis. From a reductionist, bottom-up approach represented by the SMT the consensus is moving toward an emergentist, top-down and bottom-up approach where the centerpiece of the research effort is the tissue microenvironment. A rapidly growing body of

data on stroma-epithelium interactions and the role of mechanical forces on tissue architecture suggest that cancer is a developmental process, akin to organogenesis but gone awry, happening at the tissue level of biological complexity. No amount of rhetorical fodder will resolve the paradoxes emerging when explaining carcinogenesis and metastasis. Systems biologists now have the tools at the *in animal, in culture* and the *in silico* levels and the ingenuity to devise new methodologies aimed at unraveling this complex process. However, for this to be effective it will be crucial to honor evolutionary principles; as not even organismal biology could be understood outside the frame of evolution [17,67]. In our view, the questions we are left to grapple with are the following: 1) is the default state of *all* cells *proliferation* or *quiescence*? and 2) is the locus of carcinogenesis the *tissular* level of biological organization or, instead, the *cellular/subcellular* one? The answers to these questions ought to enlighten the scientific community on the merits of joining evolutionary thinking at levels of biological complexity that have so far escaped its powerful influence. The overused mantra of "translational research" would then make more sense and thus replace hype with substance.

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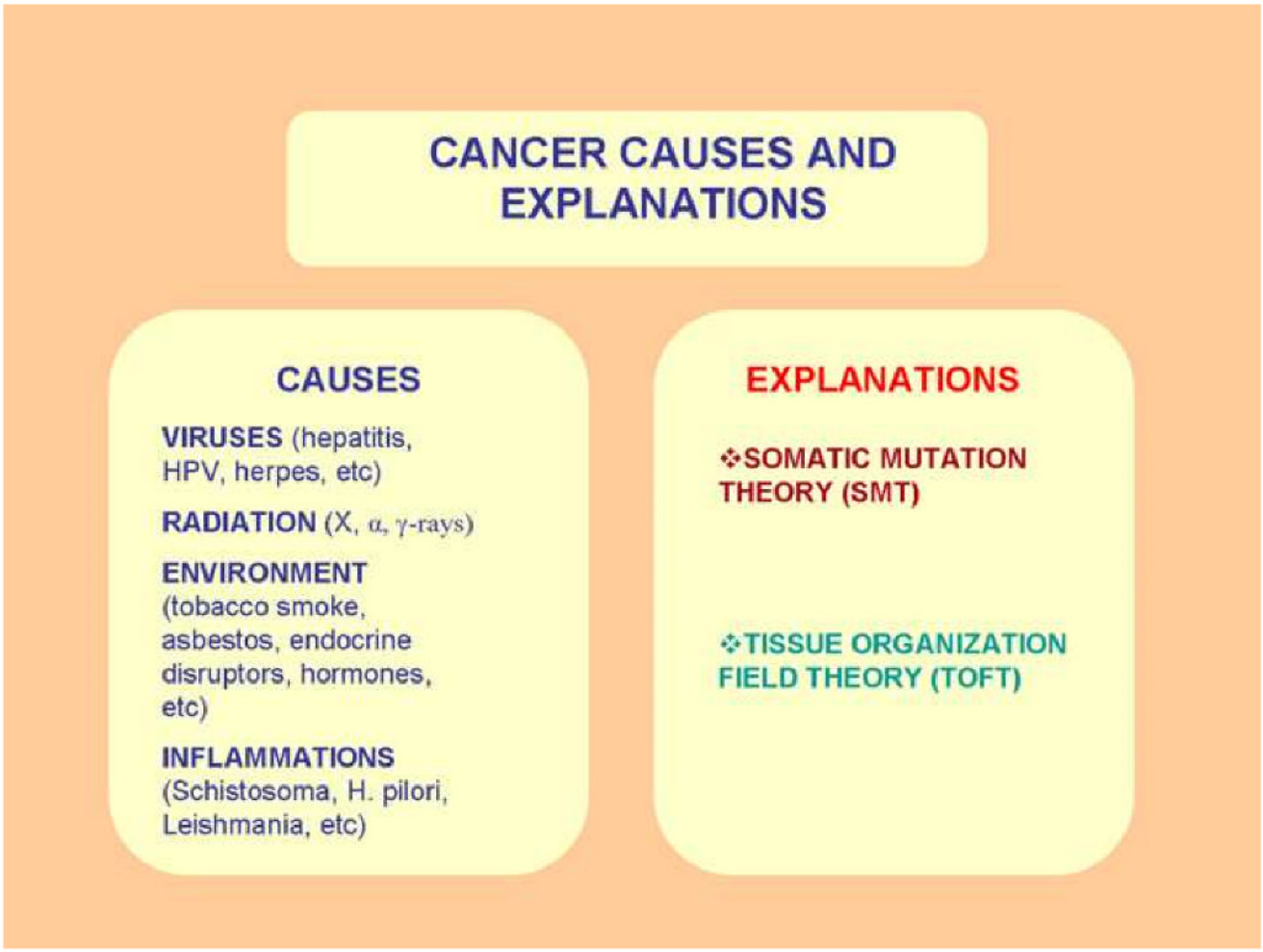

FIGURE 1.
Differences between the terms “Causes” and “Explanations’ in the context of cancer research.