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RESEARCH HIGHLIGHTS

Cancer-causing somatic mutations: they are neither necessary nor sufficient

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Abstract

For over a century, the somatic mutation theory of carcinogenesis (SMT) has been adopted by researchers as the theory of record to explain the vast bio-medical implications of the cancer disease. Central to this theory is the notion that mutated alleged cancer genes are responsible for the cancer phenotype(s). Despite generous sustained funding and unwavering research commitments, the presence and the roles of genomic mutations remain undefined and controversial. Our analysis of the merits of causatively linking mutated cancer genes and cancer phenotypes suggests that such mutations are neither necessary nor sufficient.

Keywords: T somatic mutation theory, cell proliferation, quiescence, cancer, tissue organization field theory

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> Science is impelled by two main factors, technological advance and a guiding vision. A properly balanced relationship between the two is key to the successful development of a science: without the proper technological advances the road ahead is blocked. Without a guiding vision there is no road ahead; the science becomes an engineering discipline, concerned with temporal practical problems
>
> (Woese, 2004)

> All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have or to post-pone the action that it appears to demand at a given time
>
> (Bradford Hill, 1965)

1. Introduction

Explanations of how cancers begin, progress and end have mostly relied on the somatic mutation theory of carcinogenesis (SMT) narrative that since 1914 posited that cancer was due to a defect at the level of the nuclear chromatin of a single cell (Boveri, 1914). All along, cancer was considered to be a *cell-based* disease, which in turn implied that neoplasms were monoclonal. Originally, the SMT challenged the then current view proposed by German pathologists during the last decades of the 19th century when cancer was considered a *tissue-based* disease (Triolo, 1965). During the second half of the 20th century, the SMT became the hegemonic theory of carcinogenesis (Nowell, 1976; Cairns, 1975). Meanwhile, beginning in the 1960s, the increasingly refined technology brought about by the molecular biology revolution contributed to solidifying the rationale inherent in the SMT to explain neoplasia and to develop treatments.

2. The building of the SMT hegemony

The hegemony of the SMT was predicated during the second half of the last century and the current one through definitive pronouncements by cancer researchers and commentators in the scientific literature and in

biology textbooks whose authors adopted the premises of this theory. For instance, the cancer cell was considered to be "A renegade cell" (Weinberg, 1998). More recently, it has been said that "We now know precisely what causes cancer: a sequential series of alterations in well-defined genes that alter the function of a limited number of (*intracellular*) pathways" (Sansregret and Swanton, 2017). For all practical purposes, cancer became known as a disease of cell proliferation; concomitantly, defects in the cell cycle components, signaling and gene expression were aggressively studied because they were also assumed to be crucial for carcinogenesis (Alberts et al. 2014;Weinberg 2014b). Additionally, declarative statements such as "Cancer arises through the sequential accumulation of mutations in somatic cells" (Drost *et al.*, 2017), "It is now widely accepted that cancer is the result of the gradual accumulation of driver gene mutations that successively increase cell proliferation" (Tomasetti et al. 2017), "Every cancer originates from a single cell." (Roerink *et al.*, 2018) or still "All cancers are caused by somatic mutations; however, understanding of the biological processes generating these mutations is limited" (Alexandrov *et al.*, 2013) T.N.became representative of this Zeitgeist. In fact, alleged "mutations in the transforming DNA" have been construed as "conclusive evidence" for considering cancer as a molecular and genetic disease (Stratton *et al.*, 2009;Martincorena and Campbell 2015). Some even have recently predicted that "pathology labs will give up their microscopes altogether in favour of instruments that rapidly sequence DNA and proteins and identify metabolites" (Ledford 2017) and others have been echoing these views (Kalinich and Haber, 2018); efforts in this direction, though criticized, are already underway (Cohen et al. 2018;Prasad et al. 2018). Equally influential, the hegemony of the SMT is currently being popularized in magazines and newspapers that spread the message that "cancer arises from mutations,…" (May, 2018). Notwithstanding, a minority of cancer researchers (Huang, 2014;Joyner *et al.*, 2016; Tannock and Hickman, 2016; Hanahan, 2014; Weinberg, 2014a; Brock and Huang, 2017; Yaffe, 2013) as well as some in the lay community (Macilwain, 2015; BBC, 2018) claim that the above-referred forewarnings are stubbornly refusing to materialize. To overcome these interpretative conflicting views, over the years, those siding with the reductionist approach inherent to the cell-based SMT have generated a series of *ad hoc* course corrections mostly involving the micro-environment surrounding the alleged original mutated cancer cell (Ye and Weinberg, 2015; Merlo *et al.*, 2006; Lloyd et *al.*, 2016). Notwithstanding, the direct causal role(s) of the above referred somatic mutations in carcinogenesis remains unproven. This essay focuses its attention on the role, if any, that somatic mutations may play in carcinogenesis. We will not address the controversy about "what exactly is a gene?" since it has been comprehensively addressed elsewhere (Rheinberger *et al.*, 2015; Fox-Keller, 2001; Moss, 2003; Gerstein *et al.*, 2007).

3. Causation in biology and cancer

Keeping in mind the musings of A. Bradford Hills as surmised in one of the epigrams of this Commentary, we will briefly address the controversial topic of causation in biology. In order to do so it is worth starting with modern physics, whereby invoking causal links has been mostly replaced by invoking invariants: that is, the conservation of these invariants is grounded on the idea that the 'laws' of physics are the same at different positions and times. For example, at the time of its inception classical mechanics invoked theoretical causes; namely, it proposed a fundamental principle, that of inertia. This principle states that if no cause (such as a force) modifies the properties of an object, the object conserves its properties. To the contrary, when moving to the biological sciences, living objects (i.e., unicellular and multicellular organisms) have the distinctive ability to initiate activity by themselves, and thus change their properties or states even in the absence of an external cause. This property is referred to as *agency*; it manifests itself by the ability of the living to reproduce and move, which are the salient properties of organisms (Sonnenschein and Soto, 1999). This ability of living organisms to be agents challenges the classical notion of cause as an external stimulus. Thus, from this abbreviated analysis, a clear difference can be established between the inert and the alive regarding what happens to them when not acted upon. Thus, while in classical mechanics the default state is known as *inertia,* its equivalent default state in biology is *proliferation with variation and motility* (Longo *et al.*, 2015; Soto *et al.*, 2016).

Another difference between physical and biological objects is that the latter are specific historical objects. That is, they are individuals and they result from the historical processes of ontogenesis and phylogenesis. In contrast, physical objects are generic and ahistorical (Longo *et al.*, 2015). In physics, a theoretical cause

represents an invariant with respect to all pertinent contexts. Instead, in an experimental biology context, what usually is called a cause should more properly be described as a differential cause. This is illustrated by typical experiments whereby one group of animals is treated with a hormone and another similar group with the vehicle alone. This difference in treatment affects the expression of a phenotype in a contextual manner. Although experimentalists would intuitively attribute the noticeable effect to the hormone, in reality what is being measured is a difference, and thus, at best, this perturbation would be a differential cause. In order to learn about the theoretical cause underlying the differential cause it would be necessary to find out how the latter affects the constraints on the system. This desire is satisfied when a suitable theoretical frame becomes available (Longo *et al.*, 2015; Longo and Soto, 2016). Due to the present impossibility of identifying theoretical causes in biology, heretofore we will use quotation marks to distinguish a differential cause (i.e., "cause") from a proper theoretical cause.

A few additional caveats will help in providing perspective to our analysis. Given that the default state is a principle, it does not require an explanation. Returning to the relevance of defining causation in biology, because organisms are agents, their default state is a cause in biology. To the contrary, anything that affects the default state is a constraint (Longo *et al.*, 2015; Soto *et al.* 2016). In this context, constraints are factors that may change the range of potential phenotypes of a living being. These constraints may either enable or hinder a given phenotype.

Leaving aside momentarily the interpretative difficulties mentioned above, and taking into consideration that the SMT is relying on "causes" such as mutations, a pragmatic way to deal with the problem of causation in either cancer research, or in any field where causal chains are invoked within a reductionist framework, it would be legitimate to use the notions of *necessary and sufficient* whereby… "Necessary (N) expresses "what is needed", while sufficient (S) expresses "what meets the need" for something to occur. Necessary becomes what is required in a compulsory fashion, indispensable and not susceptive of being waved. Sufficient is instead what is enough, adequate and unwilling to tolerate any more of something" (for a more extended analysis of the concept of causality in experimental biology see (Gomez-Marin 2017)). Parenthetically, these notions do not apply to non-reductionist, non-mechanicist theoretical frames (Gomez-Marin, 2017; Longo *et al.*, 2012; Longo *et al.*, 2015; Gilbert and Sarkar, 2000). Thus, using the reductionist and mechanicists framework embedded in the SMT and the empirical evidence we and others have collected, we may now address the question… *Are somatic mutations necessary and/or sufficient to generate neoplasia?* In other words, does the SMT meet criteria of causality applicable to the conceptual framework that it embraces?

4. Do "driver" somatic mutations cause cancers?

Table 1 represents a schematic summary of the available evidence regarding the hypothetical role attributed to somatic mutations in carcinogenesis. All along the last century and the current one, numerical (aneuploidy, heteroploidy) and structural (insertions, deletions, translocations, etc.) chromosomal and genomic (point mutations, inversions, etc.) aberrations were the main criteria for claiming that differences existed between what were perceived as "normal" and "cancer" cells (Heim and Mitelman, 1987; Rowley and Mitelman, 1993; Sansregret and Swanton, 2017). In this regard, a thorough analysis of over 10,000 solid tumors confirmed that ~ 90% of them were aneuploid; however, genomic analysis of these cancers now under the sponsorship of the TGCA concluded that, other than a correlation, the role of aneuploidy in tumorigenesis remains a mystery (Weaver and Cleveland, 2006; Taylor *et al.*, 2018). By overtly adopting the SMT, cancer researchers assumed that somatic mutations would unambiguously explain carcinogenesis with the subsequent accrual of diagnostic, prognostic and therapeutic benefits to patients (Longo and Soto 2016). However, the absolute explanatory value of the alleged oncogenes and suppressor genes on carcinogenesis described in the last five decades has been pointedly criticized even by those who aggressively postulated their existence (Bishop, 1991; Weinberg, 2014a; Sonnenschein and Soto, 2017; Lazebnik, 2010). Separately, now from a methodological perspective, confirming or denying that somatic mutations play a sufficient and/or necessary role in carcinogenesis faces significant shortcomings (Kato *et al.*, 2016; Krimmel *et al.*, 2016). Thus, leading cancer researchers and commentators have unambiguously admitted failure when attempting to causally link a role of somatic mutations and the cancer phenotype.

	Predicted-NECESSARY		Predicted-SUFFICIENT		EMPIRICAL	
Cells	NORMAL	CANCER	NORMAL	CANCER	NORMAL	CANCER
Non-mutated	yes/no	no	yes	no	yes/no	yes/no
Mutated	yes/no	yes	no	yes	yes/no	yes/no

Table 1. Predicted outcome for necessary or sufficient criteria vs. empirical data on mutations.

5. Somatic mutations in normal cells and in cells present in "benign" lesions

In the last decade, high-throughput DNA sequencing techniques have been instrumental in determining that most neoplasms carry anywhere between 1000 and 20,000 somatic point mutations (Vogelstein *et al.* 2013). Remarkable technological marvels have also allowed for a detailed analysis of over tens of thousands of cancer exomes and whole cancer genomes which, in turn, have led to the identification of alleged "cancer genes". Moreover, due to the now ready availability of inexpensive versions of these powerful techniques, normal control cells (namely, cells present in healthy tissues from both healthy humans and cancer patients) have also been shown to carry similar mutations in those same alleged "cancer genes" (Martincorena and Campbell, 2015; Jamshidi *et al.*, 2017; Gatenby, 2017). It is thus evident that somatic mutations are ubiquitous in normal cells of "healthy" multicellular organisms (Lupski, 2013; Ju *et al.*, 2017; Dal *et al.,* 2014; Acuna-Hidalgo *et al.,* 2015). For instance, somatic mutations were found in brain cells of neuropsychiatric patients (McConnell *et al.,* 2017). Also, multiple somatic mutations in alleged "cancer genes" were found in "normal" cells from otherwise asymptomatic men and women (Martincorena and Campbell, 2015; Krimmel *et al.*, 2016). Additionally, women suffering from endometriosis carry alleged "driver" mutations in cells that belong to deep infiltrating endometriosis lesions (26%) of the epithelial compartment; however, these lesions are virtually at no risk of malignant transformation (Anglesio *et al.,* 2017). Altogether, somatic mutations including those present in alleged cancer genes can be found in normal somatic cells, in cells that are present in neoplasms and in benign tumors (Kato *et al.*, 2016; Krimmel et al. 2016; Yadav *et al.*, 2016; McKerrell *et al.,* 2015).

These results suggest that mutations may be necessary but not sufficient to participate in carcinogenesis (see Table 1).

6. "Cancer cells" that do not carry somatic mutations in alleged cancer genes

In certain childhood tumor types such as medulloblastoma, neuroblastoma and rhabdoid tumors, few or none of the "cancer driving gene" mutations have been detected (Versteeg, 2014). Also, whole genome sequencing of posterior fossa ependimomas did not reveal mutated genes or translocations, or epigenetic aberrations (Parker *et al.,* 2014; *Mack et al.,* 2014). Some cancers are made up of clonal populations that have few or no mutated genes (Burrell and Swanton, 2016). Thus, empirical evidence indicating that there are malignant neoplasms in which somatic mutations remain undetected suggests that mutations are neither sufficient nor necessary to generate neoplasms (Table 1).

7. Additional evidence against somatic mutations causing cancers

As has been incisively pointed out over a century ago by Boveri, it is not feasible to observe cancer during its initial stages; therefore, theories are proposed to explain what may have happened early on but cannot be empirically verified. Boveri's original chromatin damage explanation later morphed into somatic mutations that in clinical cancers could be plausibly considered as a consequence rather than a cause of the disease. Additionally, reports that normal cells carry mutations in alleged driver cancer genes are increasingly acknowledged (Martincorena and Campbell, 2015; Jamshidi *et al.*, 2017; Krimmel *et al.*, 2016; Jaiswal *et al.*, 2014; McKerrell *et al.*, 2015). As elegantly put by R. Prehn "it may be more correct to say that cancers beget mutations than it is to say that mutations beget cancers" (Prehn, 1994). The advent of whole genome sequencing has generated strong evidence consistent with Prehn's dictum.

8. If somatic mutations are neither necessary nor sufficient to generate a neoplasm, is it time to abandon the SMT?

Toward the end of the 1960s, at the time the War on Cancer program was being hatched, the American geneticist Francisco J. Ayala was arguing for the autonomy of biology by stressing the need for incorporating the explanatory power of teleology in biological systems, particularly in the framework of evolutionary theory. Ayala also made a distinction between common sense and science by arguing that "…science proposes explanatory hypotheses that must be testable, i.e. accessible to the possibility of rejection or falsification'' (Ayala, 1968). In this context, after four decades of aggressive financial and manpower efforts, thought-leaders in the cancer field have unambiguously admitted failure when explaining cancer by the SMT (Weinberg, 2014a). This state of affairs justifies seriously considering Ayala's sensible epistemologically-based recommendations. So far, however, when facing this reality, a substantial fraction of the cancer research community reacts either by a) denying this state of affairs (Vaux 2011), b) offering additional *ad hoc* course corrections while stubbornly retaining the somatic mutational component of the SMT (Merlo et al. 2006;Lloyd et al. 2016;Ye and Weinberg 2015;Chen et al. 2017) and/or, regretfully, c) offering no significant theoretical alternative.

9. Alternatives to solve the Cancer puzzle

But… have alternatives to the SMT been offered? Two decades ago, the text of the 1999 book, THE SOCIETY OF CELLS (Sonnenschein and Soto, 1999), offered an alternative to the SMT by proposing the adoption of the Tissue Organization Field Theory of carcinogenesis (TOFT). Briefly, the TOFT frontally challenges the relevance of the SMT by positing, instead, that cancer is a) a *tissue-based* disease and b) that the default state of all cells is *proliferation with variation and motility*. Shortly thereafter, the merits of the SMT and the TOFT and the empirical results were simultaneously tested and provided evidence favoring the latter (Maffini *et al.*, 2004). Moreover, contrary to implications of the SMT, cancers can be reversed when placing epithelial cells derived from rat mammary gland adenocarcinomas into the "cleared" fat pads of syngeneic rats not exposed to a carcinogen (Maffini *et al.*, 2005). These data plus those reported by others as well as evolutionarily-relevant theoretical considerations challenge the validity of the SMT and more specifically the plausibility that somatic mutations "cause" cancer (Versteeg, 2014; Soto and Sonnenschein, 2011; Mintz and Ilmensee, 1975; McCullough *et al.*, 1998; Bizzarri and Cucina, 2016; Hendrix *et al.*, 2007; Bussard *et al.*, 2010; Baker, 2015; Montévil and Pocheville, 2017; Brock and Huang, 2017) (for an extended analysis see (Bertolaso, 2016)).

Additional contributions have opened the possibility of initiating an alternative research program based on robust, evolutionarily-relevant premises that may well suit the needs of the biomedical community. Simultaneously, based on the novel perspective offered by the TOFT, the treating oncologist may start considering Cancer under a more realistic context where a comprehensive personal and societal-based prevention policy combined with the principle of "*primum non nocere*" may overcome the decades-old approach of treating cancer as the enemy that will only be vanquished under a scorch-earth therapeutic regime (Brock and Huang, 2017).

10. Conclusions

The theoretical explanations and the empirical evidence collected on carcinogenesis ought to be integrated within the broad context of organogenesis. In this regard, we have proposed that cancer represents "development gone awry" and that somatic mutations ("driver" or otherwise) are neither necessary nor sufficient to cause cancers. The quantity and quality of the data collected so far at the cellular, tissue and organismic levels of biological organization justifies making an informed decision about the worthiness of a) abandoning the SMT and its *ad hoc* course-corrections, b) adopting the TOFT, or c) proposing alternative cancer theories.

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