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THE CANCER PUZZLE: WELCOME TO ORGANICISM

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Abstract

During the fifty years since President Nixon declared the "War on Cancer", those inside and outside the cancer community have witnessed the systematic moving of the goalposts attitude to accommodate evidence into an inadequate theory, that is, the Somatic Mutation Theory (SMT). This sorry state promoted a renewable yearly promise that at the end of the next 10-year period the promises uttered in 1971 would become reality. Each failure triggered calls to do more of the same research under the same theory, routinely using more and more sophisticated technology. Meanwhile, in the last few years, an unambiguous general consensus has emerged acknowledging that this overall long, intensive effort has failed, and that it is likely that the solution to the cancer problem resides elsewhere, namely, in alternative theoretical principles of biology. In this essay we concentrate, first, on the big picture, from the philosophical stance (reductionism versus organicism) to the need to adopt rigorous theories. From this novel perspective we conceptualize cancer as a disease of tissue organization akin to development gone awry. Finally, having identified both a promising stance and a useful theory, i.e., the tissue organization field theory (TOFT), we call for abandoning the SMT and for adopting the more promising TOFT.

Keywords

cancer; tissue organization field theory; somatic mutation theory; organicism; reductionism

EPIGRAPHS

"What we need most at present is to develop an autonomous science of organismal organisation, the social science of the human body: a science not so naive as to suppose that its units, when isolated, will behave exactly as they do in the context of the wholes of which they form a part, and willing to recognise that whole functioning organisms are its proper concern. It will try to explain normal growth,

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AUTHORS STATEMENT

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> differentiation, maintenance, and repair, as well as their disorders. It will take biological orderliness in action as its field of study. It lies, in wait for a name, between cytology and sociology. It is much more than oncology, for it is the study of the organisation of whole organisms as well as that of disorganisational tumour formation. It is biocybernetics, the science of organismal organisation, the study of the foundation of life. It is this subject which must take over from "cancer research", which-- by its very title--proclaims its limitations and which, through lack of fruitful governing ideas, has become too diffuse to be effective. It is in any case only the tail end of a subject and one which has lost its way searching for a non-existent goal. It must restate the very aims to which it is committed."
>
> (Smithers 1962a)

> "Theories never proceed from facts. Theories only proceed from previous theories, often very old ones. Facts are only the route (rarely direct) by which theories proceed from one to another."
>
> (Canguilhem 2008)

1. Introduction

Neoplasia means new growth. Probably the most representative definition of neoplasm is that of R.A. Willis which stated: "A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after cessation of the stimulus which evoked the change" (Willis 1967). After more than a century of research, definitions of neoplasia are plagued with inconsistencies stemming from our imperfect grasp of the biological process that underlies its genesis. However, the hallmark of neoplasms is altered tissue organization and excessive accumulation of cells. Pragmatically, neoplasms are diagnosed by pathologists, and only by pathologists, using light microscopes. Because neoplasms only arise in multicellular organisms, and for the most part look histologically like a caricature of the organ of origin, it seems natural to address the problem of carcinogenesis as morphogenesis gone awry. In fact, this was the perspective adopted by the German pathologists who studied cancer during the second half of the 19th century (Triolo 1964, 1965).

Historians, philosophers and biologists addressed the overall changes in the practice and conceptualization of biological phenomena that took place in the 19th and 20th century (Mayr 1996, Gilbert and Sarkar 2000, Soto and Sonnenschein 2018). Among them, the philosopher Lenny Moss described a turning point that imposed a choice "... between a theory of life which locates the agency for the acquisition of adapted form in ontogeny...versus a view that expels all manner of adaptive agency from within the organism and relocates it in an external force—or as Daniel Dennett (1995) prefers to say, an algorithm called 'natural selection'" (Moss 2003). Because of this change, agency, normativity and individuation, as well as teleological explanations hitherto considered the main characteristics of the living, almost disappeared from biological language. In fact, teleology, that is, explaining something as a function of its goals, was offensive to scientists embracing mechanicist stances (Peluffo 2015, Mayr 1961). In Jacob's own words: "For a long time the biologist has been consorting with teleology as with a woman without

whom he can't live, but with whom he doesn't want to be seen in public. To this hidden relationship, the concept of program gives a legal status" (Jacob 1973). Since then, cells and organisms became passive recipients of a program. In sum, the program and information metaphors hindered the study of embryology because they ignored the important role of the environment in the determination of phenotypes and in developmental plasticity.

The transfer of agentive properties to molecules other than genes, such as hormones, has also created an image of cells and organisms as the passive result of internal (genes, hormones, etc.) and external agents (natural selection) (Soto and Sonnenschein 2018). As a consequence of this phylogenetic turn, biologists concentrated their attention on the cell rather than the organism and adhered to mechanist explanations leaving behind the circular causality linking the organism with its parts. Another consequence of the phylogenetic turn has been the internalization of natural selection as if the cells in the organism were totally autonomous entities. Currently, this mechanistic and reductionistic stance is actively being contested both by philosophers and biologists who are bringing back agency and teleology as *bona fide* biological concepts.

Before addressing the characteristics of cancer that cannot be explained by the reductionist perspective offered by the somatic mutation theory (SMT), we will take a short detour to describe the differences between these two stances, namely, the one centered on the organism, and the other on the cell. Many of these incompatibilities were apparent 60 years ago and were addressed in an excellent critique by the renowned oncologist David W. Smithers published in The Lancet entitled "An attack on cytologism". In it, he identified various lacks of fit between the SMT and clinical cancer observations. His cogent criticism is as relevant today as it was at the time of its publication (Smithers 1962b, Soto and Sonnenschein 2020). The epigraph quoted above succinctly suggests what needs to be done to integrate cancer into the organism where it may either thrive or regress. We will end our analysis by presenting an alternative to the SMT, originally proposed 20 years ago, namely, the tissue organization theory (TOFT), that addresses the many incompatibilities identified by Smithers.

2. Reductionism versus organicism

Reductionist stances, which dominated biology during the last two centuries, are usually derived from an ontology of unchanging substances, that is, of "being", which characterizes classical mechanics. Organicist stances, instead, are usually focused on an ontology of "becoming" (Dupré and Nicholson 2018). There are three types of reductionisms, namely, ontological, epistemic, and methodological: i) Ontological reductionism (physicalism) claims that organisms are made up of molecules and their interactions; this is the worldview of the practitioners of the other two kinds; ii) Epistemic reductionism claims that higher-order phenomena (organismic, for example) can be reduced to more basic levels, such as those of chemistry and physics. The consequence of this brand of reductionism is that biology cannot be considered an independent science. And iii) methodological reductionism is the idea "that biological systems are most fruitfully investigated at the lowest possible level, and that experimental studies should be aimed at uncovering molecular and biochemical causes" (Brigandt and Love 2017). These reductionist notions imply that

molecular biology can, in principle, fully explain all biological facts, and that based on these tenets, causality ought to be explored using a bottom-up approach.

The alternative stance that we favor, organicism, has its philosophical roots in Aristotle, who has been considered the first biologist (Aristotle 1934). Two millennia later, Immanuel Kant underscored the interrelatedness of the organism and its parts, and the circular causality implied by this relationship. Teleological judgment was described as an organizing principle that allows for the explanation of the biological object through its unity (this object being the cause and effect of itself), before giving a discrete description of its parts (Kant 2000). During the 20th century, this stance was further developed by the organicist movement (Sonnenschein and Soto 2018). According to Nicholson and Gawne, during the second half of the 20th century, organicists shared a commitment "to three general ideas...: (a) the centrality of the organism concept in biological explanation; (b) the importance of organization as a theoretical principle; and (c) the defense of the autonomy of biology" (Nicholson and Gawne 2015).

According to Gilbert and Sarkar, organicism is a materialistic philosophical stance that, contrary to reductionism, considers both bottom-up and top-down causation (Gilbert and Sarkar 2000). Still, other organicists explain emergence without invoking downward causation, making organicism compatible with the dominant current of analytical philosophy (Mossio, Bich, and Moreno 2013). In sum, today organicism represents a suitable stance to guide the study of development, physiology and physiopathology.

3. The role of theory

Scientists acknowledge that they are inside the world they wish to observe and study. As a result of this realization, objectivity must be constructed through scientific theories that would provide intelligibility principles to frame observations, experiments and explanations. Theories thus play both an important and practical role in scientific practice: they determine what can be observed, and hence the type of experiments that could be performed within the frame proposed by the theory. The importance of theory could be summarized by the motto attributed to Ludwig Boltzmann: "Nothing is more practical than a good theory". However, this applies only to precisely stated theories; vague theories are of no practical utility because they cannot be proven wrong (Feynman 2017).

4. In search of a theory of organisms

The quoted-above epigram taken from Smithers' 1962 article denotes a need for a theory comprising the whole life cycle of living beings. To fulfill this void, we recently proposed 3 principles for a Theory of Organisms (Soto, Longo, Miquel, et al. 2016), namely: a) a principle of biological inertia, represented by the default state (proliferation with variation and motility) (Soto, Longo, Montévil, et al. 2016, Montévil, Mossio, et al. 2016); b) the principle of variation (Montévil, Mossio, et al. 2016), and finally c) the principle of organization (Mossio, Montévil, and Longo 2016).

The default state provides a link between the theories of organisms and of evolution. The common ancestor of all living organisms had to necessarily be a cell that proliferated

constitutively. With the advent of sexually reproducing multicellular organisms, individuals developed from a zygote, which is simultaneously an organism and a cell (Soto, Longo, Montévil, et al. 2016). Ontogenesis occurs under theoretical principles that govern cell behavior: cells are normative agents that initiate actions, such as expressing their default state of proliferation and motility, which figure prominently in the process of carcinogenesis and metastasis (Sonnenschein and Soto 1999). In addition, proliferation generates variation because cell division results in two similar but not identical daughter cells (Soto, Longo, Montévil, et al. 2016). Cellular and supra-cellular *variation* generate the relentless changes that occur throughout the organism's lifespan producing individuation, plasticity and novelty (Montévil, Mossio, et al. 2016). The principle of *organization* addresses the stability of organisms by the interdependence of vital processes, technically referred to as "closure of constraints" (Mossio, Montévil, and Longo 2016). These principles provide a framework whereby normal development and its alterations, including carcinogenesis, can be conceptually understood, experimentally explored and mathematically modeled (Montévil, Speroni, et al. 2016). These fundamental principles frame the tissue organization field theory (TOFT), that treats carcinogenesis as a problem of tissue organization, comparable to organogenesis.

5. Cancer as a problem of faulty morphogenesis

Generally, for the skilled pathologist, the histological structure of a carcinoma resembles its organ of origin. Like the structure of normal organs, the cancerous tissue contains a parenchyma and a stroma. In normalcy, the parenchyma performs the functions of the organ while the stroma is supposed to play the role of scaffolding and of conduit for the blood and nerve supply of the organ in question. During organogenesis the role of the mesenchyme includes specifying spatial organization (Sengel 1976), cytodifferentiation of the epidermal derivatives, and induction of specific patterns of branching morphogenesis (Sakakura, Nishizuka, and Dawe 1976, Bernfield, Cohn, and Banerjee 1973). The reciprocal interactions of mesenchyme and epithelium have been mapped in detail in kidney organogenesis: in this case, while the mesenchyme induces branching morphogenesis of the ureteric bud the ureteric bud induces the mesenchyme to undergo nephrogenesis (Grobstein 1956, Davies 2002) and cytodifferentiation. Remarkably, cytodifferentiation of mesenchymal derivatives does not occur in the absence of the ureteric bud. This phenomenon is not limited to *de novo* morphogenesis but is also demonstrable during adulthood. Indeed, like the mesenchyme during organogenesis, the adult stroma plays a central role determining the structure and function of epithelial structures (Cunha et al. 1985). From this background, it follows that altered morphogenesis also implies altered interactions among tissues (Hayward et al. 2001, Maffini et al. 2004).

6. Where does cell agency fit within the metazoan organism?

As briefly outlined above, we have proposed a biological principle, the *default state of proliferation with variation and motility*, which is common to all prokaryotic and eukaryotic cells; clearly, this statement includes all unicellular organisms and those that form part of multicellular ones. It is also evident that each cell division brings about an unequal number

of molecules in each cell, thus resulting in similar but not identical cells; this is the source of variation acknowledged by the default state principle.

As with the concept of inertia in classical mechanics, proliferation, variation and motility, require no explanation in biology. To the contrary, hindrances to the expression of the default state, namely, proliferative quiescence, lack of variation, and lack of movement are the ones that require an explanation (Longo and Soto 2016, Longo et al. 2015). Despite the assertion that principles need not be tested, data supporting this principle are available (Soto and Sonnenschein 1985, Sonnenschein, Soto, and Michaelson 1996, Yusuf and Fruman 2003, Ying et al. 2008).

7. Studying carcinogenesis as faulty organogenesis

Several biologists expressed the believe that data “speak by themselves”; however, data carry theoretical baggage, regardless of whether or not the researcher is aware of this fact (Dennett 1995). For example, in the field of mammary gland carcinogenesis a widely held assumptions is that experimental exposure to a chemical carcinogen directly causes to mutations in the DNA of a cell in the mammary epithelial tissue. However, when the carcinogen is injected into an animal all the cells in the organism are exposed, not just the epithelial mammary cells. Another widely held assumption is that the alterations of tissue architecture observed in the resulting neoplasms are a direct consequence of this primary mutational event. However, if one is guided, instead, by the idea that carcinogenesis is equivalent to organogenesis gone awry, these two assumptions become irrelevant.

We experimentally tested both views at once by using a mammary tissue recombination model and the chemical carcinogen nitrosomethylurea (NMU) in order to identify the primary target of the carcinogen. Objectively, we aimed to determine in a single experimental design whether the target of the carcinogen is a cell in the epithelium as alleged by the SMT, the stroma as proposed by the tissue organization field theory (TOFT), or both tissue compartments, an outcome that would not rule out either theory. Mammary epithelial cells were exposed *in culture* either to the carcinogen or vehicle before being transplanted into the cleared fat pads of rats exposed to carcinogen or vehicle. Carcinomas developed only when the stroma was exposed *in vivo* to NMU, regardless of whether or not the epithelial cells were exposed to the carcinogen. Mammary epithelial cells exposed *in vitro* to the carcinogen formed phenotypically normal ducts when injected into a non-treated stroma. Mutation in the Ha-*ras*-1 gene did not correlate with initiation of neoplasia. Not only was a mutation in the Ha-*ras*-1 gene often found in both cleared mammary fat pads of vehicle-treated animals and intact mammary glands of untreated animals, but it was also absent in some tumors. These results highlight the conclusion that the stroma is the crucial target of the carcinogen and that mutation(s) in the Ha-*ras*-1 gene is/are neither necessary nor sufficient for tumor initiation (Maffini et al. 2004).

8. Reversibility and normalization of neoplasms

Clinical regression is not just the disappearance of the neoplastic tissue; overt neoplasms may undergo a path to tissue normalization. For example, malignant neuroblastomas

spontaneously become benign ganglioneuromas, a phenomenon documented many times since 1927 (Smithers 1969). More recently, it was reported that Schwann cells in the stroma normalize neuroblastomas by inducing maturation of neuroblasts into non-proliferating ganglion cells (Ambros et al. 1996). Moreover, some experimental neoplasms referred to as "conditional neoplasms" spontaneously regress. For example, tar-induced tumors in rabbits (Rous and Kidd 1941, Smithers 1969) usually regress after cessation of tar application, and the Scharlach orange-induced tumors regress when the stain is progressively removed by macrophages (Bullock and Rohdenburg 1915). Thus, spontaneous cancer regression is a process of remodeling of the cancerous tissue and the consequent "normalization" of the cells inside it (Sonnenschein and Soto 2020). Also, conclusions drawn from the classical experiments by Mintz and Ilmensee in the 1970's (Mintz and Ilmensee 1975) and additional ones reported since then buttress the notion that normalization is an experimentally reproducible fact (Kasemeier-Kulesa et al. 2008, Frank-Kamenetskii and Booth 2019) amply documented in clinical settings.

Experimental reversibility is a well-studied phenomenon which has been documented in several distinct models. Probably the most impressive of them is the normalization of embryonal carcinoma cells injected into blastocysts, their incorporation into various tissues of the resulting mice, and the ability of these mice to produce fertile gametes derived from the cancer cells (Mintz and Ilmensee 1975). In general, these experiments consist of the isolation of cells from a neoplasm that clinically classifies as "malignant". Here, the aim is to normalize these cells by placing them in close contact with cells in the normal organ of origin of the neoplasm. Successful examples of this protocol are rat hepatocarcinomas into the liver (McCullough et al. 1998), and rat mammary carcinoma into a clear mammary fat pad (i.e., the mammary gland stroma)(Maffini et al. 2005), or the mixing of the neoplastic cells with normal cells of the organ of origin followed by tissue recombination (Frank-Kamenetskii and Booth 2019). So far, cells carrying so-called oncogenes isolated from clinically "malignant" neoplasms have been shown to be normalized by normal morphogenetic fields. These series of experiments implicitly show that the concept of the "cancer cell" is erroneous. The identity of cells is determined by the structure where they reside (the tissue) by way of their developmental trajectory in the three dimensions of space and that of time.

9. Back to the usefulness of theories

As we discussed above, theories determine what can be observed, framing experiments and explanations. Moreover, the hypotheses derived from these theories, as Francisco Ayala stated "must be genuinely testable, and therefore subject to the possibility of rejection". In some instances, the "criterion of testability can then be satisfied by requiring that scientific explanations have precise logical consequences which can be verified or falsified by observation and experiment" (Ayala 1968). Within this epistemological background, it is legitimate to ask... How has the SMT fared so far?

The SMT premises are: (1) cancer is derived from a single somatic cell that has accumulated multiple DNA mutations (Weinberg 1998), (2) the default state of cell proliferation in metazoa is quiescence (Alberts et al. 2002), and (3) cancer is a disease of cell proliferation

caused by mutations in genes that control proliferation and the cell cycle[1] (Bishop 1987, Barbacid et al. 2005, Varmus and Weinberg 1992). By adopting the SMT, the researcher obligatorily focuses on the interior of cells, searching for DNA mutations and stimulators of cell proliferation and of motility in order to explain tumor growth, invasion and metastasis. Because mutations are practically permanent, under these premises, cancer is considered irreversible. However, the SMT framework is confronted by evidence showing the presence of mutated oncogenes (Martincorena and Campbell 2015), aneuploidy in normal tissues (Martincorena and Campbell 2015, Mishra and Whetstine 2016), and with neoplasms containing neither gene mutations nor epigenetic aberrations (Versteeg 2014). The evidence shows, instead, that somatic mutations are neither necessary nor sufficient for cancer to develop (Sonnenschein and Soto 2018). Additionally, the normalization of the neoplastic phenotype, both ascertained clinically and experimentally, argues that "the cancer cell" does not exist *per se* (Sonnenschein and Soto 2011).

During its long dominance in the field of cancer research and medical practice, the contradictions that threatened the foundations of the SMT were temporarily bridged by means of *ad-hoc* fixes. Early on, a single mutated gene (oncogene) was considered sufficient to explain carcinogenesis. This was soon proven insufficient and *ad hoc* adjustments were successively proposed. Thus, those researchers that thought that a single gene mutation was sufficient to explain carcinogenesis added more gene mutations to obtain the same effect. Then, not only proliferation but also apoptosis had to be involved (Soto and Sonnenschein 2011, Baker 2014). Recently, mutations in putative oncogenes were found in normal cells of normal tissues (Martincorena et al. 2015). These fixes have now reached the point of paradigm instability (Baker 2015). As stated by the philosopher JA Marcum, regarding the attitude of supporters of the SMT, reductionists "... are constantly expanding their notion of reductionism to account for the complexity of cancer – as they continue to investigate the cause(s) of the disease – is there a limit to how much they can extend this presupposition until no further extension is possible or effective? In other words, will future anomalies arise that cannot be resolved by expanding reductionism, by including more genes or even cells? The issue, according to organicists, is whether there is a limit to reductionist biology for obtaining a full explanation of cancer..." (Marcum 2005). This addition of ideas derived from organicist perspectives makes the SMT even more vague and contradictory. As discussed above, a vague theory cannot be proven wrong (Feynman 2017). The SMT fulfils this categorization.

10. Conclusions

Almost sixty years ago Smithers stated, "Observation has produced too many incompatibilities, and a vast research effort too little support, for conventional cancer theory

[1]The somatic mutation theory does not address hereditary cancer transmitted by the germline. Germline mutations affect every cell in the organism, and thus hereditary cancer could also be interpreted as due to faulty tissue interactions in morphogenetic fields (Sonnenschein, Davis, and Soto 2014). An illustrative example is the development of tumors in Drosophila unambiguously linking a germline mutation to the emergence of a neoplasia. Having characterized the mutated gene, however, has shed little light on how mutations in this gene result in the formation of a tumor. Neuroblastomas appear in larvae carrying homozygous mutations of a gene called lethal giant larva-2 (lgl-2). The normal gene codes for an intracellular, cytoskeleton-associated protein expressed in the early embryo, long before the morphogenesis of the nervous system takes place. Tumor prevention was achieved by introducing a normal copy of l(2)gl into the genome of l(2)gl deficient animals (Strand et al. 1991).

to hope to hold its place much longer". Our analysis of the theoretical bases under which cancer research has been conducted for the last century, as well as the massive amount of data collected during this long period revealing more contradictions and incongruities, buttresses Smithers evaluation of the SMT. The time has come to finally abandon the SMT and to embrace a theory that adopts reliable principles relevant to the theories of evolution and of organisms, i.e., the TOFT (Sonnenschein and Soto 1999, 2016). This radical necessary change is long overdue, as already noted by Smithers, and will have profound effects in biology at large. Regarding cancer, it will bring this disease back to where it belongs, i.e., the study of dysfunctional organogenesis and regeneration, this time acknowledging the centrality of the organism.

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