HHS Public Access

Author manuscript

Prog Biophys Mol Biol. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

Prog Biophys Mol Biol. 2016 October ; 122(1): 70–76. doi:10.1016/j.pbiomolbio.2016.07.004.

Carcinogenesis explained within the context of a theory of organisms

Carlos Sonnenschein and

Centre Cavaillès, École Normale Supérieure, Paris, France, and Institut d'Etudes Avancees de Nantes, France and Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, Boston, MA USA

Ana Soto

Centre Cavaillès, République des Savoirs, CNRS USR3608,, Collège de France et Ecole Normale Supérieure, Paris, France and Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, Boston, MA USA

Abstract

For a century, the somatic mutation theory (SMT) has been the prevalent theory to explain carcinogenesis. According to the SMT, cancer is a cellular problem, and thus, the level of organization where it should be studied is the cellular level. Additionally, the SMT proposes that cancer is a problem of the control of cell proliferation and assumes that proliferative *quiescence* is the default state of cells in metazoa. In 1999, a competing theory, the tissue organization field theory (TOFT), was proposed. In contraposition to the SMT, the TOFT posits that cancer is a tissue-based disease whereby carcinogens (directly) and mutations in the germ-line (indirectly) alter the normal interactions between the diverse components of an organ, such as the stroma and its adjacent epithelium. The TOFT explicitly acknowledges that the default state of all cells is *proliferation with variation and motility.* When taking into consideration the principle of organization, we posit that carcinogenesis can be explained as a relational problem whereby release of the constraints created by cell interactions and the physical forces generated by cellular agency lead cells within a tissue to regain their default state of *proliferation with variation and motility.* Within this perspective, what matters both in morphogenesis and carcinogenesis is not only molecules, but also biophysical forces generated by cells and tissues. Herein, we describe how the principles for a theory of organisms apply to the TOFT and thus to the study of carcinogenesis.

Corresponding Author: Carlos Sonnenschein, Centre Cavaillès, École Normale Supérieure, Paris, France, and Institut d'Etudes Avancees de Nantes, France. and Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, Boston, MA USA. carlos.sonnenschein@tufts.edu.

The authors have no competing financial interests to declare.

Keywords

Tissue organization field theory; default state; closure; organicism; stroma epithelium interactions

> "Theories never proceed from facts. Theories only proceed from previous theories, often very old ones."
>
> –Georges Canguilhem, Knowledge of Life

> "The human mind delights in finding pattern—so much so that we often mistake coincidence or forced analogy for profound meaning. No other habit of thought lies so deeply within the soul of a small creature trying to make sense of a complex world not constructed for it."
>
> — Stephen Jay Gould, The Flamingo's Smile: Reflections in Natural History

1. Introduction

Since Aristotle, living objects were referred to in terms of teleology and circular causality. These properties of the living were further addressed by Kant in the 18th century, and were successfully adopted by the teleomechanists as a proper heuristic for the understanding of biological phenomena. This causal circularity and interdependence between the organism and its parts was clearly different from the reductionist perspective of Newtonian mechanics. Since then, and before the term "organicism" was created, this organicist view was adopted by an increasing number of biologists. By the mid-19th century, encouraged by the early success of organic chemistry elucidating some aspects of digestion and nutrition, there were biologists that opted for a reductionistic perspective. However, research in biology was then centered on the organism, its development and plasticity, exemplified by the discovery of polyphenism and environmental determination of phenotypes. This is the tradition to which belonged the pathologists that studying cancer in the last half of the 19th century who considered this disease to be a problem of defective tissue architecture.

The early 20th century is marked by what Lenny Moss called the "phylogenetic turn", that is, the passage from the idea that the agency for the acquisition of adapted form resides in the organism and its ontogeny, to the idea that it should be sought in phylogeny. The agency thus relocates in an external force, natural selection. "As the genetic program moved to the explanatory center stage, the individual organism, with its own adaptive capacities, began to recede from view."(Moss 2003) The re-discovery of Mendelian genetics and the introduction of Darwinism are linked to this change; admittedly, the reductionism brought about by the phylogenetic turn reached its zenith with the dominance of the modern synthesis. This early-20th century perspective shifted the attention from organisms to cells, as reflected by the introduction of cell-tissue culture techniques, and most particularly, genetics. This theoretical shift affected all biological fields, including cancer.

For over the last one hundred years, cancer has occupied a privileged position among the diverse diseases that have plagued humans by virtue of its perceived uniqueness. In the first five decades of the last century, cancer and infectious diseases shared the special attention of

physicians and biologists, as well as that of the public at large. However, with the advent of effective antibiotics against bacterial infections and tuberculosis (penicillin and streptomycin, respectively), cancer became the center of attention for a significant portion of the biomedical community. By midcentury, two main competing cancer theories were already being proposed to explain the disease. They were addressing the cancer problem at different levels of organization: one regarded cancer as a cell-based disease (centering mostly on the control of cell proliferation), while the other regarded cancer as a tissue-based disease (focusing on altered morphogenesis).

The cell-based theory is known as the somatic mutation theory (SMT); its paternity is assigned to Theodor Boveri who, in his original 1914 German-language version of his book, proposed that at its core the cancer problem was located inside the nucleus of a normal cell that acquired changes in its chromatin that somehow would convert it into a cancer cell. Boveri insightfully maintained that it was impossible to observe the cancer process at what he called *statu nascendi:* this truism is still valid today. Soon after, the development of a tumor mass was attributed to mutations in this cancer cell that made it proliferate autonomously skipping organismal control (Boveri 1914;Boveri 1929;Triolo 1964). Ever since, the main premise of the SMT has been that cancer is a cell-based disease and implicitly, it acknowledged that the default state of cells in multicellular organisms was *quiescence.*

Theodor Boveri's original version of the SMT represented a significant departure from the viewpoint dominant in the late 19th century among German pathologists who considered that cancer was a tissue-based disease (Triolo 1964). In 1936, Conrad Waddington and John Needham briefly elaborated on this tissue-based perspective and posited that cancer was, instead, a process akin to abnormal development (Waddington 1935;Needham 1936). This tissue-based alternative to the SMT remained as a minority view on the subject and did not receive much support until later in the 20th century.

Soon after the midcentury, and more specifically, after the momentous discoveries that followed what is dubbed as the Molecular Biology Revolution, the SMT attracted the focused attention of the cancer research community. This gigantic research program adopted a reductionist strategy that followed the original SMT premise, i.e. cancer is a cell- and gene-based, molecular disease. Early warnings regarding this interpretation of data were dismissed or ignored, and research proceeded, and still does, under those epistemological arguments. Among early skeptics, David W. Smithers published an impassionate critique in 1962 which maintains its relevance in the present day; entitled "An attack on cytologism;" it exposed the shortcomings of the SMT and proposed, instead, that cancer is a problem of tissue organization (Smithers 1962). Today, even the most ardent backers of the SMT and the War on Cancer effort have acknowledged that the promised explanations of cancer and its eventual cure have not materialized (Weinberg 2014;Hanahan 2014;Sonnenschein and Soto 2013).

After having spent almost three decades working on the control of cell proliferation in multicellular organisms, in 1999, we proposed an alternative theory of carcinogenesis that we called the tissue organization field theory (TOFT) (Sonnenschein and Soto 1999). Ever

since, our theory has challenged the hegemony of the SMT to explain cancer while adopting an organicist perspective; in this context, our attention was focused on the level of biological organization at which the subject of inquiry, cancer, is being observed, namely, the tissue level and thus, as a problem of tissue organization akin to histogenesis and organogenesis (Sonnenschein and Soto 2008;Soto and Sonnenschein 2011). From our perspective, carcinogenesis is a process analogous to embryonic development, whereby organs are constructed through interactions among different cell types; in short, this means that cancer is a relational problem (see below). Equally important, if not of greater impact in biology at large, we explicitly incorporated into the TOFT the basic premise that *proliferation with variation and motility* is the default state of *all* cells. The implications of adopting this premise have been highlighted in separate articles of this issue.

2. Basic notions about cancer as a human disease

Before considering the relationship between the TOFT and the theory of organisms, a brief account of the general subject of cancer in humans is in order.

2.1 What is cancer?

The hallmarks of neoplasms are altered tissue organization and excessive accumulation of cells. For almost two centuries, neoplasms have been and are still diagnosed by pathologists, who base their diagnoses on those above-mentioned two main hallmarks.

2.2 Classifications of cancers

Neoplasms have been classified by a number of criteria. From a *clinical* perspective, they have been classified as a) benign and b) malignant. The former are perceived as circumscribed, with limited borders and non-invasive. In this context, benign tumors are made up of cells that do not metastasize at a distance through blood or lymphatic vessels. While this descriptive property may be satisfactory to some, it should be understood that an increasingly expanding benign tumor may be lethal if it seriously compromises the function of a neighboring organ or tissue. Malignant neoplasms, to the contrary, are tumors that invade their local surroundings (neighboring stroma), become motile and anchor in near or distant organs where they usually recapitulate the phenotypic characteristics of the primary tumor. For the most part, it is acknowledged that the incidence of successful metastases depend on whether emboli of several tumor cells or single tumor cells migrate from the primary tumor. Single tumor cells are much less efficient in generating metastases (Sonnenschein and Soto 2015).

From a *histogenetic* viewpoint, cancers have been classified into those of a) epithelial tissue origins or *carcinomas*, and those originated in b) connective tissues which includes *sarcomas* and liquid/blood-based cancers (mostly *leukemias).* Ninety percent of clinical tumors are carcinomas while the rest, just 10%, belong to the connective tissue variety.

When classifying cancers from a *pathogenetic* perspective, they fall into two main groups, namely, a) *sporadic* which are represented by over 95% of the cases for which adult cancer patients come to the clinic. By *sporadic* it is understood that their incidence is extemporaneous and that they are not obviously linked to a genetic origin. And b) *inborn*

errors of development, meaning cancers that affect mostly young patients which cover the rest of the population (less than 5%). Within this group we have identified two sub-groups, one of which we call i) *inherited inborn errors of development* (less than 2% of cancer patients) that affect mostly young patients who carry mutations in all their cells because they were conceived by the fusion of mutated gametes (parental sperm and/or a maternal oocyte). There is a second sub-group that we call ii) *induced inborn errors of development* represented by cancers that arise due to the effect of carcinogens acting on embryonic or fetal morphogenesis. It is assumed that no alleged cancer-associated mutations were present in the gametes of the parents of this latter group. We anticipate that as more statistical data will be gathered on tumors in this latter group, their incidence will increase while that of the *sporadic* ones will decrease proportionally (Sonnenschein et al. 2014).

3. Premises of the TOFT

In order to explain carcinogenesis, the TOFT adopts two main premises, namely, a) *cancer is a tissue-based disease* akin to the process of morphogenesis during development (cancer is *development gone awry*), and b) *proliferation with variation* and *motility* is the default state of all cells (Soto and Sonnenschein 2011). The latter principle, *proliferation with variation* and *motility* represents a fundamental biological postulate (i.e., equivalent to that of *inertia* in physics) and hence, it does not require an explanation. This principle is implicit in the Darwinian view of evolution. What requires an explanation is the identification and mode of action of the constraints that limit the instantiation of the default state both in unicellular and in multicellular organisms. Regarding multicellular organisms, how these constraints are modified enabling the proliferation and motility of cells is a central issue for the understanding of morphogenesis and tissue repair; these are processes taking place in tissues, organs and organisms of both normal and diseased individuals, included cancer stricken patients. Adopting proliferation and motility as the default state of all cells makes it unnecessary to search for stimulators of both proliferation (i.e., the so-called growth factors, and oncogenes) and of cellular movement and migration. Proposing a default state then provides a founding principle for a theory of organisms while playing the pragmatic role of framing observations and experiments. Although theoretical principles do not require experimental observation for their formulation, they frame experimental conditions under which empirical data can reproducibly show a pattern of exponential proliferation which closely fit the default state (Soto and Sonnenschein 1984; Wray et al. 2010;Ying et al. 2008;Sirbasku and Moreno-Cuevas 2000)(Soto et al, this issue).

4. The theory of organisms and its impact when explaining development

The fundamental biological principles we proposed for the construction of a theory of organisms are interdependent. They are a) the default state (proliferation with variation and motility) (Soto et al, this issue), b) the principle of organization which addresses the generation and maintenance of stability by closure of constraints (Mossio et al, this issue) and c) the principle of variation, which is generated both at the cellular and supracellular levels.

Central to a theory of organisms is the cell theory. Multicellular organisms start their life cycle as a cell, i.e., the zygote. Phylogenetically, all living organisms are supposed to have originated from a common ancestor, the last universal common ancestor, called LUCA. This common ancestor must have been endowed with the capacity to proliferate constitutively, that is, without having to be actively stimulated by something or someone. It then follows that cells are agents and thus can initiate actions, such as proliferation and movement. Variation is generated inside cells by the process of cell division which propagates variation by generating two similar but slightly different daughter cells. A cascade of phenotypic changes takes place all along the lifespan of individual organisms. This incessant symmetry breaking generates individuation and novelty while the principle of organization brings stability by closure of constraints (Mossio et al, this issue). In other words, during morphogenesis and tissue repair the organism undergoes changes in the form of successive transformations of organization states (Longo et al. 2015).

Theories and their principles are not only useful to provide explanations of biological phenomena, but also help in framing both *in vivo, in culture, ex vivo* and *in silico* experiments. The ensemble of the three principles constitutes the bases for developing a mathematical model of morphogenesis. This model has already shown that constraints to the default state are sufficient to explain ductal and acinar formation in the mammary gland (Montévil et al this issue). This exercise validates a proof of concept that normal development and its alterations can be conceptually understood from the theory of organisms and that its principles provide a theoretical framework for further experimental testing.

5. The theory of organisms and the TOFT

Once the principles of our theory of organisms have been identified, it becomes relevant to ask how, when and where does carcinogenesis fit within this theory. The TOFT proposes that carcinogenesis, like morphogenesis, is a relational problem. What do we mean by relational? An example from embryology, namely, the development of the kidney illustrates our point. Interactions between its two precursor tissues, the ureteric bud and the metanephrogenic mesenchyme, generate the reciprocal induction between the collecting system (derived from the ureteric bud) and of the nephron (derived from the metanephrogenic mesenchyme). Neither one of these tissues, in the absence of the other, can generate a functioning kidney. However, when placed together they originate a nephron and a collecting system. Moreover, the metanephogenic mesenchyme cells when placed alone are unable to cytodifferentiate into the 10 cell types they generate when they interact with the ureteric bud (Lehtonen and Saxén 1986;Gilbert and Sarkar 2000). From this and various other examples of organogenesis (lung, salivary and mammary glands, teeth, etc.), we conclude that relational interactions among different components of an organ cannot be reduced to discrete sub-cellular events (Gilbert 2013). In fact, morphogenesis, which is the generation of shape and form, is inextricably linked to physical forces generated by these cell-cell and cell-tissue interactions (Shyer et al. 2013).

The model of mammary gland morphogenesis resulting from the principles outlined above had a cellular component, i.e., the epithelial cells, and a physical component, a matrix which

contains collagen fibers. Unless constrained, cells are agents that move and proliferate; they exert mechanical forces that act on the collagen fibers and on other cells. As fibers get organized, they also constrain the cells on their ability to move and to proliferate. The model exhibits a circularity that can be interpreted in terms of a closure of constraints. Executing this mathematical model revealed that constraints to the default state are sufficient to explain ductal and acinar formation. Furthermore, it suggests an additional target of research, namely, new constraints generated by the epithelial cells such as inhibitors of cell proliferation and motility. It is then plausible that alterations of these constraints are at the root of carcinogenesis. For example, it was found that excess rigidity of the tissue gives rise to irregular structures unable to form a lumen, which are reminiscent of carcinoma *in situ* (Paszek et al. 2005). This finding is consistent with the observation that mammographic density, which is due to enhanced tissue rigidity, is a risk factor for breast cancer. We posit that the loosening of any of the constraints described in the morphogenesis model may lead to abnormal tissue organization, and if persistent, to carcinogenesis.

A widely used model in carcinogenesis consists of the treatment of normal, young female rats from susceptible strains with a chemical carcinogen (i.e., nitrosomethylurea, NMU, etc.) or a physical one like radiation. In the following few months, all or nearly all these animals develop mammary adenocarcinomas. Where does the chemical or the radiation ultimately act to induce cancer? Or, in other words, which is the target of the carcinogen? We adopted a theory neutral approach to test whether the target of the carcinogen was either any of the cells in the epithelium, as proposed by the SMT, or relational, namely, the interactions among stroma and epithelium and their cells. In our case, we exposed separately the stroma and the epithelium of rat mammary glands to a carcinogen having a short half-life (~20 min). The former group became the “exposed” group, while the group of rats exposed to the vehicle used to administer the carcinogen became the “non-exposed” group. Once the carcinogen was “cleared” from the “exposed” group (that is, five days after carcinogen exposure), four recombinants between epithelium and stroma were performed. The recombination of exposed stroma with normal non-exposed epithelial cells resulted in adenocarcinomas, which originated in the epithelial ducts. The reverse combination did not generate tumors in their hosts (Maffini et al. 2004). Subsequently, we reported the normalization of epithelial tumor cells isolated from NMU-induced mammary carcinomas which organized as normal mammary gland ducts when injected into normal mammary gland stroma (Maffini et al. 2005). Similar outcomes were obtained from recombining a quasi-normal, non-tumorigenic mammary epithelial cell line and irradiated stroma (Barcellos-Hoff and Ravani 2000), and a non-tumorigenic prostate cell line and prostate cancer derived fibroblasts (Barclay et al. 2005). Altogether, this empirical evidence was consistent with explanations advanced by the TOFT and inconsistent with those of the SMT. Moreover, these experiments contradict the idea that cancer is irreversible as implied by the dictum “once a cancer cell always a cancer cell.” (Pierce et al. 1978).

6. Using the TOFT to explain “cancer puzzles”

Next, we focus our analysis by examining evidence collected in the field of cancer that has been perceived as representing quirks or “cancer puzzles.” This characterization was based on the difficulty in interpreting outcomes of experimental protocols using the genocentric

approach of the SMT. Among those puzzles, it is worth recalling instances where, on the one hand, normal tissues transplanted into the “wrong” locations resulted in neoplasia while, on the other, genuine cancer tissues and their cells became normalized after being placed in the midst of normal tissues (normal niches). Perhaps one of the most spectacular of those puzzles is exemplified by a series of experiments spanning 8 years whereby Leroy Stevens transplanted early mouse embryos into the testis of congenic mice. These embryos generated local teratocarcinomas that were eventually transplanted for almost 200 generations from mouse to mouse. The normalization of these teratocarcinoma cells was described in a series of articles published in the 1970s by a group of researchers under the leadership of Beatrice Mintz (Mintz and Ilmensee 1975;Illmensee and Mintz 1976;Stewart and Mintz 1981). Transplantation of these teratocarcinoma cells into early blastocysts of mice resulted in viable offspring that showed a mosaic phenotype combining tissues derived from both the host’s normal cells and the grafted teratocarcinoma cells. Some of these teratocarcinoma cells in the mosaic male mice ended up randomly in their testis, contributed to the germ line and formed sperm which carried the genes of these formerly teratocarcinoma cells into their own progeny. The conclusions we have drawn from the teratocarcinoma experiments and comparable ones are that a cell from a neoplasm behaves as a normal cell does, both regarding its proliferative capability (both a normal and a cell belonging to a neoplasia generate two, and only, two daughter cells) and in its ability to carry a genome that responds to cues from distant or neighboring cells and extracellular matrix as a normal cell does (Sonnenschein and Soto 2011). Thus, the conclusions drawn from experiments conducted by us and by others are compatible with the notion that genuine neoplastic tissues and cells are able to generate normal cells and tissues when grafted among normal cells. This finding contradicted once again the implicit message of the SMT that “once a cancer cell, always a cancer cell.” (Pierce et al. 1978).

Now, if as posited by the SMT, neoplasia is due to the accumulation of multiple stable mutations in a single cell (Nowell 1976), how can it be explained that this stably mutated neoplastic cell and its progeny can be restored to behave as a normal cell? For one, it is probabilistically unlikely that random reverse mutational events could have “repaired’ the genomic somatic mutations allegedly responsible for their generating a cancer phenotype. Secondly, the switch from neoplasia to normalcy in animals has unambiguously been shown to be bidirectional. Namely, cells from an embryo may generate neoplasms when placed outside their normal, original habitat (i.e., early embryos placed inside the testis, or in the peritoneum) while when these neoplastic cells are placed back into a normal morphogenetic field they reacquire a fully normal phenotype (see above). In any case, the proliferative and the motile behaviors of individual somatic cells in the midst of tissues depend on whether or not the microenvironment they inhabit enables them to express their constitutive ability to proliferate and/or move. All along the successive normal developmental stages in which multicellular organisms are engaged, the ability of each cell to proliferate, create variation and move are constrained by interactions with their neighboring cells, the tissue in which they reside and the organism as a whole. These constraints are functional; that is, they undergo closure and thus contribute to the stability of the system.

A comparable parsimonious argument can be offered when explaining the occurrence of cancers in offspring resulting from the fusion of mutated parental gametes (sperm and/or

oocytes). These neoplasms are what we have described above as *inherited inborn errors of development* (Sonnenschein and Soto 2015). In such offspring, all the cells in the respective morphogenetic fields of the conceptus carry those genomic mutations. Those mutations may occur in genes whose protein products participate in the establishment of normal morphogenetic fields, and thus, morphogenesis will be impaired and this "development gone awry" may end up forming a neoplasm which would manifest postnatally as an organ malformation or a tumor or both. Examples of these rare *inherited inborn errors of development* are the Li-Fraumeni syndrome, retinoblastoma, BRCA 1 and 2-linked breast and ovarian tumors, the Lynch syndrome, and other rare syndromes. Indeed, these syndromes due to germ-plasm mutations represent less than 2% of all clinical tumors. In carriers of these germ-line mutations, all the cells of the individual are mutated and thus the morphogenetic field as a whole reflects the underlying defect in these syndromes. In this context, it becomes relevant to state that the tumors or malformations in these offspring are the result of alterations in the development of morphogenetic fields in which all of their constituent cells are mutated. In these instances, mutations become "proximate" causes of the malformations and/or tumors.

Separately, the other sub-group of *induced inborn errors of development* can be generated when carcinogens (such as environmental endocrine disruptors, viral or radiation exposure, etc.) affect embryos during organogenesis (Sonnenschein et al. 2014). The evidence already collected in this field is consistent with the notion that in addition to the above-referred documented instances of *inherited and induced inborn errors of development*, a good percentage of *sporadic* cancers (about 98% of all clinical cancers) may have been initiated in the womb(Soto and Sonnenschein 2010;Paulose et al. 2015). In any case, the origin of all these cancers regardless of whether they are due to germ-line mutations or the deleterious effects of carcinogens during morphogenesis can be explained as due to the underlying process of *development gone awry* (Soto and Sonnenschein 2011).

Phenotypes of epithelial cells are susceptible of being manipulated experimentally by changing the niche (epithelium/stroma) in which they originally land or are placed. In addition to the examples cited above from B. Mintz and her group, those of Barcellos-Hoff and Ravani (Barcellos-Hoff and Ravani 2000) and ours (Maffini et al. 2005), others have strengthened this concept. For instance, when mouse mammary tumor virus (MMTV)-"neu-induced" tumor cells mixed with normal mammary mouse epithelial cells were inoculated into cleared mammary fat pads (stroma), these cells were normalized and found to form normal ducts together with the normal epithelial cells (Booth et al. 2011). In addition, these "tumor cells" differentiated into normal luminal, myoepithelial and secretory mammary epithelial cells. Thus, a normal mammary microenvironment, comprised of stromal, epithelial and host-mediated constraints, may combine to suppress the cancer phenotype during glandular regeneration.

Next, we provide additional examples of how data that do not fit explanations proposed by the SMT can be easily incorporated into the context offered by the TOFT.

6.1 Spontaneous regression of neuroblastoma

This childhood neoplasm is probably the one with the highest documented rate of spontaneous regression (Brodeur 2003). The rigorously documented regressions of these cancers include even some classified as stage 4S, which metastasize to the liver, skin, and/or bone marrow. Cell and tissue differentiation and apoptosis are central to the regression process that has been verified to end up as mature ganglion cells and Schwann cells during adulthood (Haas et al. 1988). This outcome contradicts the notion that “malignant” neoplasms are unresponsive to physiological apoptotic signals and that unrestrained proliferation stimulated by mutated gene products (oncogenes and suppressor genes) makes alleged cancer cells practically autonomous and thus, unable to be reversed. The changes in tissue architecture observed during regression of this tumor type are fully compatible with explanations proposed by the TOFT.

6.2 Regression of hormone-sensitive tumors and their metastases

Breast and prostate tumors are another example of tumors that are not autonomous given that these tumors may regress after gonadectomy or chemical hormonal ablation. Hormone antagonists (and in some cases agonists such as diethylstilbestrol, in the case of breast carcinomas) have been shown to induce apoptosis and regression as well (Huggins 1967;Jordan et al. 2009;Debruyne 2002). These features raise doubts about the predictions anticipated by the SMT, whereby mutations in hypothetical oncogenes and suppressor genes result in unrestrained (autonomous) cell proliferation.

6.3 Normalization by regulation of tissue architecture

Cancer cells may reverse their “malignant” properties when placed among normal tissues. Examples of this cases include teratocarcinoma cells injected into blastocysts, as referred to above (Mintz and Ilmensee 1975), embryonal carcinoma cells injected into the mammary gland (Bussard et al. 2010), highly malignant melanoma cells injected into Zebra fish embryos (Kasemeier-Kulesa et al. 2008), mammary carcinoma cells recombined with normal mammary gland stroma (Maffini et al. 2005), hepatocarcinomas injected into normal liver (McCullough et al. 1997), etc. are examples where the premises adopted by the TOFT can reconcile empirical data with carcinogenesis theory.

6.4 Foreign body carcinogenesis

A number of inert substances (asbestos, plastics, etc.) embedded in tissues of susceptible animal hosts generate tumors locally (Baker 2015;Bischoff and Bryson 1964); the SMT does not successfully account for examples of foreign-body carcinogenesis. Substances like metals, asbestos, plasticware, do not release genotoxic compounds that might mutate the DNA of a neighboring cell. Invariably, these tumors show changes on local tissue architecture, a result consistent with the TOFT.

7. Conclusions

Twenty years ago we were puzzled by the lack of theoretical coherence in the fields of control of cell proliferation and cancer. After having proposed that proliferation and motility is the default state of all cells, including those in metazoans, we extended our theoretical

exploration to carcinogenesis which led us to propose the TOFT, whereby cancer is considered as a tissue-based disease. We have explored this alternative to the hegemonic SMT using a theory-neutral experimental protocol that simultaneously tested the TOFT and the SMT. Results of this test favored adopting the TOFT and rejecting the SMT.

Understanding cancer requires paradigmatic changes which are incompatible with the reductionist, genocentric perspective of the molecular biology revolution at large and the SMT in particular. While the theory of evolution provides increasingly adequate explanations of phylogeny, biology still lacks an identifiable theory of organisms that would encompass ontogeny and life cycles. Throughout this issue, aiming at achieving that goal, we proposed three principles, namely, a) a default state, b) a principle of variation and c) one of organization. Using these principles, we have argued that carcinogenesis can be explained as a relational problem whereby release of the constraints created by cell interactions and the physical forces generated by cellular agency lead cells within a tissue to regain their default state of proliferation with variation and motility. Ultimately, carcinogenesis defined as development gone awry now fits well with the principles we propose for a theory of organisms.

Acknowledgments

This work was conducted as part of the research project ‘Addressing biological organization in the post-genomic era’, which was supported by the International Blaise Pascal Chairs, Region Ile de France. Additional support was provided by Award Number R01ES08314 from the National Institute of Environmental Health Sciences to AMS. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors are grateful to Cheryl Schaeberle for their critical input.

References

Baker SG. A cancer theory kerfuffle can lead to new lines of research. J Natl Cancer Inst. 2015; 107:dju405. [PubMed: 25528755]

Barcellos-Hoff MH, Ravani SA. Irradiated mammary gland stroma promotes the expression of tumorigenic potential by unirradiated epithelial cells. Cancer Res. 2000; 60:1254–1260. [PubMed: 10728684]

Barclay WW, Woodruff RD, Hall MC, Cramer SD. A system for studying epithelial-stromal interactions reveals distinct inductive abilities of stromal cells from benign prostatic hyperplasia and prostate cancer. Endocrinology. 2005; 146:13–18. [PubMed: 15471963]

Bischoff F, Bryson G. Carcinogenesis through solid state surfaces. Prog Exp Tumor Exp Tumor Res. 1964; 5:85–133.

Booth BW, Boulanger CA, Anderson LH, Smith GH. The normal mammary microenvironment suppresses the tumorigenic phenotype of mouse mammary tumor virus-neu-transformed mammary tumor cells. Oncogene. 2011; 30:679–689. [PubMed: 20890308]

Boveri, T. Zur Frage der Entstehung Maligner Tumoren. Fischer; Jena: 1914.

Boveri, T. The Origin of Malignant Tumors. Williams & Wilkins; Baltimore MD: 1929.

Brodeur GM. Neuroblastoma: Biological insights into a clinical enigma. Nat Rev Cancer. 2003; 3:203–216. [PubMed: 12612655]

Bussard KM, Boulanger CA, Booth BW, Bruno RD, Smith GH. Reprogramming human cancer cells in the mouse mammary gland. Cancer Res. 2010; 70:6336–6343. [PubMed: 20647316]

Debruyne F. Hormonal therapy of prostate cancer. Seminars in Urology Oncology. 2002; 3(Suppl 1):4–9.

Gilbert, SF. Developmental Biology. Vol. 10. Sunderland: Sinauer Associates, Inc; 2013. http://10e.devbio.com/article.php?id=23&search=genetics

Gilbert SF, Sarkar S. Embracing complexity: Organicism for the 21st century. Developmental Dynamics. 2000; 219:1–9. [PubMed: 10974666]

Haas D, Ablin AR, Miller C, Zoger S, Matthay KK. Complete pathologic maturation and regression of stage IVS neuroblastoma without treatment. Cancer. 1988; 62:818–825. [PubMed: 3293764]

Hanahan D. Rethinking the war on cancer. Lancet. 2014; 383:558–563. [PubMed: 24351321]

Huggins C. Endocrine-induced regression of cancers. Science. 1967; 156:1050–1054. [PubMed: 5337357]

Illmensee K, Mintz B. Totipotency and normal differentiation of single teratocarcinoma cell cloned by injection into blastocysts. Proc Nat Acad Sci USA. 1976; 73:549–553. [PubMed: 1061157]

Jordan VC, Lewis-Wambi JS, Patel RR, Kim H, Ariazi EA. New hypotheses and opportunities in endocrine therapy: amplification of oestrogen-induced apoptosis. Breast. 2009; 3:S10–S17.

Kasemeier-Kulesa JC, Teddy JM, Postovit LM, Seftor EA, Seftor RE, Hendrix MJ, Kulesa PM. Reprogramming multipotent tumor cells with the embryonic neural crest microenvironment. Dev Dyn. 2008; 237:2657–2666. [PubMed: 18629870]

Lehtonen E, Saxén L. Cytodifferentiation vs. organogenesis in kidney development. Prog Clin Biol Res. 1986; 217A:411–418. [PubMed: 2428056]

Longo G, Montévil M, Sonnenschein C, Soto AM. In search of principles for a theory of organisms. J Biosci. 2015; 40:955–968. [PubMed: 26648040]

Maffini MV, Calabro JM, Soto AM, Sonnenschein C. Stromal regulation of neoplastic development: Age-dependent normalization of neoplastic mammary cells by mammary stroma. Am J Pathol. 2005; 167:1405–1410. [PubMed: 16251424]

Maffini MV, Soto AM, Calabro JM, Ucci AA, Sonnenschein C. The stroma as a crucial target in rat mammary gland carcinogenesis. J Cell Sci. 2004; 117:1495–1502. [PubMed: 14996910]

McCullough AR, Coleman WB, Smith GJ, Grisham JW. Age-dependent induction of hepatic tumor regression by the tissue microenvironment after transplantation of noplastically transformed rat liver epithelial cells into the liver. Cancer Res. 1997; 57:1807–1873. [PubMed: 9135026]

Mintz B, Ilmensee K. Normal genetically mosaic mice produced from malignant teratocarcinoma cells. Proc Nat Acad Sci USA. 1975; 72:3585–3589. [PubMed: 1059147]

Moss, L. What Genes Can’t Do. MIT Press; Cambridge, MA: 2003.

Needham J. New advances in chemistry and biology of organized growth. Proc Roy Soc B. 1936; 29:1577–1626.

Nowell PC. The clonal evolution of tumor cell populations. Science. 1976; 194:123–128.

Paszek MJ, Zahir N, Johnson KR, Lakins JN, Rozenberg GI, Gefen A, Reinhart-King CA, Margulies SS, Dembo M, Boettiger D, Hammer DA, Weaver VM. Tensional homeostasis and the malignant phenotype. Cancer Cell. 2005; 8:241–254. [PubMed: 16169468]

Paulose T, Speroni L, Sonnenschein C, Soto AM. Estrogens in the wrong place at the wrong time: Fetal BPA exposure and mammary cancer. Reprod Toxicol. 2015; 54:58–65. [PubMed: 25277313]

Pierce, GB., Shikes, R., Fink, LM. Cancer: A Problem of Developmental Biology. Prentice-Hall; Englewoods Cliffs, NJ: 1978.

Shyer AE, Tallinen T, Nerukar NL, Wei Z, Gil ES, Kaplan DL, Tabin CJ, Mahadevan L. Villification: how the gut gets its villi. Science. 2013; 342:212–218. [PubMed: 23989955]

Sirbasku DA, Moreno-Cuevas JE. Estrogen mitogenic action. II. Negative regulation of the steroid hormone-responsive growth of cell lines derived from human and rodent target tissue tumors and conceptual implications. In Vitro Cell Dev Biol. 2000; 36:428–446.

Smithers DW. Cancer: an attack of cytologism. Lancet. 1962:493–499. [PubMed: 13914465]

Sonnenschein C, Davis B, Soto AM. A novel pathogenic classification of cancers. Cancer Cell Int. 2014; 14:113–117. [PubMed: 25493071]

Sonnenschein, C., Soto, AMAM. The Society of Cells: Cancer and Control of Cell Proliferation. Springer Verlag; New York: 1999.

Sonnenschein C, Soto AM. Theories of carcinogenesis: an emerging perspective. Seminars in Cancer Biology. 2008; 18:372–377. [PubMed: 18472276]

Sonnenschein C, Soto AM. The death of the cancer cell. Cancer Res. 2011; 71:4334–4337. [PubMed: 21507929]

Soto AM, Sonnenschein C. The aging of the 2000 and 2011 hallmarks of cancer reviews: a critique. J Biosci. 2013; 38:651–663. [PubMed: 23938395]

Sonnenschein C, Soto AM. Cancer Metastasis: So close and so far. J Natl Cancer Inst. 2015; 107

Soto AM, Sonnenschein C. Mechanism of estrogen action on cellular proliferation: evidence for indirect and negative control on cloned breast tumor cells. Biochem Biophys Res Commun. 1984; 122:1097–1103. [PubMed: 6477550]

Soto AM, Sonnenschein C. Environmental causes of cancer: endocrine disruptors as carcinogens. Nat Rev Endocrinol. 2010; 6:363–370. [PubMed: 20498677]

Soto AM, Sonnenschein C. The tissue organization field theory of cancer: A testable replacement for the somatic mutation theory. BioEssays. 2011; 33:332–340. [PubMed: 21503935]

Stewart TA, Mintz B. Successful generations of mice produced from an established culture line of euploid teratocarcinoma cells. Proc Nat Acad Sci USA. 1981; 78:6314–6318. [PubMed: 6947232]

Triolo VA. Nineteenth century foundations of cancer research origins of experimental research. Cancer Res. 1964; 24:4–27. [PubMed: 14106160]

Waddington CH. Cancer and the theory of organizers. Nature. 1935; 135:606–608.

Weinberg RA. Coming full circle-from endless complexity to simplicity and back again. Cell. 2014; 157:267–271. [PubMed: 24679541]

Wray J, Kalkan T, Smith AG. The ground state of pluripotency. Biochem Soc Trans. 2010; 38:1027–1032. [PubMed: 20658998]

Ying QL, Wray J, Nichols J, Batlle-Morera L, Doble B, Woodgett J, Cohen P, Smith A. The ground state of embryonic stem cell self-renewal. Nature. 2008; 453:519–523. [PubMed: 18497825]