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REGULAR ARTICLE

SMT or TOFT? How the Two Main Theories of Carcinogenesis are Made (Artificially) Incompatible

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Abstract The building of a global model of carcinogenesis is one of modern biology's greatest challenges. The traditional somatic mutation theory (SMT) is now supplemented by a new approach, called the Tissue Organization Field Theory (TOFT). According to TOFT, the original source of cancer is loss of tissue organization rather than genetic mutations. In this paper, we study the argumentative strategy used by the advocates of TOFT to impose their view. In particular, we criticize their claim of incompatibility used to justify the necessity to definitively reject SMT. First, we note that since it is difficult to build a non-ambiguous experimental demonstration of the superiority of TOFT, its partisans add epistemological and metaphysical arguments to the debate. This argumentative strategy allows them to defend the necessity of a paradigm shift, with TOFT superseding SMT. To do so, they introduce a notion of incompatibility, which they actually use as the Kuhnian notion of incommensurability. To justify this so-called incompatibility between the two theories of cancer, they move the debate to a metaphysical ground by assimilating the controversy to a fundamental opposition between reductionism and organicism. We show here that this argumentative strategy is specious, because it does not demonstrate clearly that TOFT is an organicist theory. Since it shares with SMT its vocabulary, its ontology and its methodology, it appears that a claim of incompatibility based on this metaphysical plan is not fully justified in the present state of the debate. We conclude that it is more cogent to argue that the two theories are compatible, both biologically and metaphysically. We propose to consider that TOFT and SMT describe two distinct and compatible causal pathways to carcinogenesis. This view is coherent with the

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existence of integrative approaches, and suggests that they have a higher epistemic value than the two theories taken separately.

Keywords TOFT · SMT · Controversy · Cancer · Pluralism

1 Introduction

The basis of the somatic mutation theory (SMT) is well known, and summarized in Hanahan and Weinberg's famous review (Hanahan and Weinberg 2000). Cancer is described as a disease caused by genetic mutations, which can be due to inherited predisposition, or to the genotoxic action of carcinogens. Recently, it was also shown that spontaneous mutations occurring during stem cells division can cause carcinogenesis, at least in some tissues (Tomasetti and Vogelstein 2015). This approach is based on various empirical evidence, and led to therapeutic success (Strebhardt and Ullrich 2008; Chabner and Roberts 2005). However, voices are rising to point out that SMT does not accurately describe the complex phenomenon of carcinogenesis. First, cancer cells often exhibit large scale genetic perturbations, with a high number of local mutations and chromosomal anomalies (Lengauer et al. 1998; Rajagopalan et al. 2003). This is contradictory with the classical version of SMT, which considers that tumorigenesis is due to punctual genetic mutations. These observations have led some authors to develop an alternative view of cancer, which have become quite influential in the last 10 years (Capp 2012). The Tissue Organization Field Theory (TOFT) was popularized by Soto and Sonnenschein in 1999 in their book *The society of cells* (Sonnenshein and Soto 1999). During a first phase, from 2000 to 2010, the advocates of TOFT published a series of articles to present and defend their description of cancer (Soto and Sonnenschein 2004, 2005, 2006; Sonnenschein and Soto 2000, 2008). During this period, TOFT was defended mainly by Soto and Sonnenschein. Their central idea is that the original cause of cancer is not genetic mutations, but disruption of tissue cohesion. This disorganization can be due to the chemical alteration of the extra-cellular matrix by carcinogens. In this perspective, the default state of the cell is not *quiescence*, but *proliferation*. As a consequence, the control of cell division vanishes when the surrounded tissues loose their structure. Soto and Sonnenschein describe the differences between the two theories as follows?: for SMT, cancer comes from a unique somatic cell which accumulated mutations of genes controlling cell cycle, and quiescence is the default state of the cell?; for TOFT, the first event of carcinogenesis is a loss of tissue organization, and not mutations in a single cell. Through this scientific description, the authors build a first biological opposition between the two approaches: *tissue* is opposed to *genes* and *proliferation* to *quiescence*.

This theory remained relatively marginal during its first 10 years. However, it has generated a more intense debate over the past few years, as shown by the recent work of Capp (Capp 2012). This author studies the history of the developments of SMT and TOFT, and proposes an *ontophylogenetic* theory which establishes links between TOFT and the random expression of the genes in a context of tissue

disruption. Notably, the year 2011 was marked by an interesting exchange of ideas in the review *Bioessays* (Vaux 2011; Soto and Sonnenschein 2011; Sonnenshein and Soto 2011; Satg 2011; Baker 2011). From 2011 up to now, the actors of the controversy have been trying to find a way out of the conflict (Baker 2012, 2013; Soto and Sonnenschein 2013; Rosenfeld 2013; Sonnenschein et al. 2014). Two radically different orientations have been chosen. A first option favors an integrative approach, which aims at building a comprehensive model of carcinogenesis taking into account all the scales involved in the process of carcinogenesis, from the gene to the tissue (Rosenfeld 2013). The second option, strongly defended by the advocates of TOFT, postulates that the two theories are incompatible, and that all attempts at conciliation would be an obstacle to scientific progress (Baker 2012). To defend this view, they use three levels of argumentation: empirical, epistemological, and metaphysical. In this article, we first analyze how these three levels are articulated. The lack of non ambiguous experimental proofs makes the first level of argumentation insufficient to irrevocably choose one of the two theories. As a consequence, we interpret the use of epistemological and metaphysical arguments as an argumentative strategy of the partisans of TOFT to be heard. More precisely, we show how they build an irreconcilable opposition between the two theories of cancer, leading to the necessity of an exclusive choice of one of them. First, they present SMT as a *regressive* program of research, to defend the need for a *paradigm shift*. We show that this view is based on an ambiguous use of the term *paradigm*, and is justified by metaphysical considerations defending a fundamental *incompatibility* between the two theories. Indeed, the partisans of TOFT assimilate the conflict between the two cancer theories to a fundamental debate between *reductionism* and *holism*. This move allows Soto and Sonnenschein to claim that "explanations of the process of carcinogenesis by these two theories belong to distinct levels of biological complexity and, therefore, are incompatible, as are their philosophical stances (reductionism versus organicism)" (Sonnenschein and Soto 2008). By linking this idea of incompatibility with the need for a paradigm shift, they purport to establish the necessity of definitively giving up SMT and adopting TOFT. Since such a claim of incompatibility has important consequences on our understanding of carcinogenesis, it is crucial to investigate whether it is justified. We show in this paper that the argumentative strategy based on the projection of the controversy on a metaphysical ground is specious and incoherent. It eliminates useful attempts at conciliation with no valid reason. By contrast, the concrete approach aiming at integrating all the scales involved in carcinogenesis seems to be more epistemologically accurate.

2 SMT or TOFT? The Role of Empirical Evidence

The articles published by the advocates of TOFT report various experimental evidence. Some of it shows, including through recombination experiments, that a stroma coming from a cancerous tissue is able to generate tumors on a healthy one, or to increase the metastatic potential of tumors cells (Smithers and Cantab 1962; Orr and Spencer 1972; Barclay et al. 2005; McDaniel et al. 2006). Other studies

investigate the influence of known carcinogens on stroma organization (Maffini et al. 2004; Barcellos-Hoff and Ravani 2000). They show that the structure of the whole tissue is sensitive to chemical molecules known for producing cancers. For the partisans of TOFT, this series of evidence is sufficient to irrevocably demonstrate the superiority of their approach. However, the adverse faction has also its say. In 2011, Vaux published an article entitled *In Defense of The Somatic Mutation Theory* (Vaux 2011). In this work, he gives three lines of evidence to support SMT. First, he raises cases of tumors which are clearly known for being due to genetic mutations, such some leukemia and lymphoma. Second, he notices that modifications of SMT were made to include new observations, notably the massive chromosomal rearrangements observed in many tumors (Stephens et al. 2011). These massive rearrangements are not well described by the classical version of SMT, which mainly considers the role of punctual mutations. Finally, the success of targeted therapies in some types of cancers is used as an argument to defend the validity of SMT. Based on the central assumption of SMT (cancer is due to genetic mutations), this therapeutic strategy tries to modify the activity of the proteins suspected to cause tumorigenesis. Consequently, the success of targeted therapy in some cancers can be considered as a relevant element to prove the validity of the genetic approach of cancer. Besides, as noticed by Soto and Sonnenschein themselves (Soto and Sonnenschein 2011), objections were made to conclusions drawn from experiments aiming at confirming TOFT. Notably, the experiments of stroma modifications of Maffini et al. (Maffini et al. 2004) and Barcellos-Hoff/ Ravani (Barcellos-Hoff and Ravani 2000) suggest the possibility of mutations affecting the cells during the protocol. Therefore, a non ambiguous demonstration of the superiority of TOFT is not easy to deliver with the current experimental methods. More importantly, it appears that both theories are supported by strong experimental arguments. For instance, the clear success of some targeted therapies is an important argument to defend SMT: the use of Trastuzumab against breast cancer presenting an overexpression of HER2 receptor is a good example (Hudis 2007). Reciprocally, the experiments of Barcellos-Hoff and Ravani (Barcellos-Hoff and Ravani 2000) bring strong arguments in favor of the TOFT approach. By modifying the molecular composition of the mammary gland stroma of mice, they show that it gained a tumorigenic potential: when recombined with non-tumorigenic epithelial cells, it induces carcinogenesis. Inversely, many observations cannot be accounted for by SMT or TOFT, taken separately.

S.Rosenfeld clearly summarizes this situation in a recent paper (Rosenfeld 2013): "Arguments in favor of both TOFT and SMT are numerous and strong (...). At the same time, a large grey zone of empirical facts and clinical cases exists which poses questions that are difficult to resolve from either of these viewpoints". As a consequence, it is difficult to find a set of empirical evidence allowing to choose one of the two theories. It is therefore problematic for the advocates of TOFT to impose their new view on empirical grounds. We suggest that this is the reason why the articles defending TOFT often mix three levels of arguments (Soto and Sonnenschein 2006, 2011; Baker 2013): empirical, epistemological, metaphysical, the two last levels being used to compensate the deficiency of the empirical demonstration. Let us see now how this is done.

3 Do We Need a *Paradigm Shift?*

"As in other instances in science, the *zeitgeist* has played a significant role in accepting untested claims of the SMT without major objections" (Soto and Sonnenschein 2011). Soto and Sonnenschein explain the domination of SMT by the popularity of the genetic approaches for describing biological phenomena. That is why the lack of evidence in favor of SMT was not an obstacle to its adoption of the somatic mutation theory. The criticism of the domination of the *genetic dogma* has been widespread since J-J. Kupiec's work (Kupiec 2000). It is used by Soto and Sonnenschein to describe SMT as a *regressive program of research* (Soto and Sonnenschein 2011). The idea is that to survive, SMT has to add ad hoc hypotheses to explain carcinogenesis. Indeed, the existence of facts that the classical versions of SMT cannot describe, such as the massive chromosomal rearrangements observed in tumors, led the defenders of SMT to make new hypothesis. The idea of *early genetic instabilities* is one of these attempts (Lengauer et al. 1998; Rajagopalan et al. 2003). Soto and Sonnenschein describe these modifications of SMT as a proof of its epistemic inferiority. But this argument is specious since TOFT itself had to evolve to take into account some empirical observations. As noted by Capp (2012), the original version of TOFT gives a negligible role to genetic mutations during cancer progression. Its ontophylogenetic theory, which can be seen as a modified TOFT approach, considers that punctual mutations or chromosomal translocations are important to describe carcinogenesis. However, Soto and Sonnenschein argue that SMT is a *regressive program of research* (Soto and Sonnenschein 2011), in Lakatos sense of the notion (Lakatos 1970): a regressive program of research is characterized by a continual need for locally adjusting the theory to experimental evidence. The advocates of TOFT add to this idea the notion of *paradigm shift* (Soto and Sonnenschein 2011; Baker 2013), which allows them to affirm the need to abandon SMT in favor of TOFT. The structure of this argument is interesting. To define the word *paradigm*, Soto and Sonnenschein use an expression taken from the famous book by the historian and philosopher Thomas Kuhn, *The Structure of Scientific Revolution (SSR)* (Kuhn 1962): a paradigm is a "universally recognized scientific achievement(s) that for a time provide model problems and solutions to a community of practitioners" (Soto and Sonnenschein 2011). However, the concept of paradigm is multiform. Different meanings can be found in Kuhn's work (in the *SRS* and in his subsequent articles), and the definition given by Soto and Sonnenschein can be considered as rather *moderate*. By using this concept, Soto and Sonnenschein can then introduce the more radical notion of *paradigm shift* (Baker 2013; Soto and Sonnenschein 2011). According to Kuhn, scientific revolutions which occurred during the history of science can be described as paradigm shifts. With this notion of paradigm, the advocates of TOFT present their theory as a new approach which has to eliminate SMT. SMT is thus considered as an old paradigm we have to give up in order to promote scientific progress (Baker 2013). But this use of the notion does not fit with the explicit definition they give. On a moderate reading of the notion of paradigm, the necessity of giving up SMT does not follow. The argument developed by the partisans of TOFT seems in fact to appeal implicitly

to the Kuhnian notion of incommensurability. When two paradigms are incommensurable, it is necessary to *adhere* to one of them, and to definitively abandon the other. The word *paradigm* then refers to a global representation of the world. In that case, indeed, when adopting a paradigm, one has to reject the others. In spite of the fact that the authors do not use explicitly the notion of incommensurability, the necessity of an exclusive choice is clearly expressed in Soto and Sonnenschein's articles: "it is left to the reader to decide whether one approach to understanding cancer appears more promising than the other" (Sonnenschein et al. 2014). Even if Soto and Sonnenschein do not speak here of a quasi religious *conversion* that characterizes the shift to a new paradigm in the radical sense of the notion, but only of rational *decision*, they nevertheless appeal to this radical meaning when defending the necessity to supersede SMT by TOFT. Indeed, they promote the adhesion to a *general system of explanation*, which is explicitly assimilated to a metaphysical position: the reader has to choose between *reductionism* and *holism* (Sonnenschein et al. 2014; Sonnenschein and Soto 2008). By using this metaphysical opposition, they can build the idea of a fundamental *incompatibility* between TOFT and SMT (Sonnenschein and Soto 2008). It is now crucial to analyze the arguments raised to defend this incompatibility.

4 Are the TOFT and SMT Incompatible?

In one of their recent papers, Soto and Sonnenschein contend that: "according to the philosopher D. C. Dennett, *there is no such thing as philosophy-free science; there is only science whose philosophical baggage is taken on board without examination*. Therefore, ignoring the philosophical underpinnings of the postulates adopted by researchers when designing experiments is bound to hinder the interpretation of the data collected. For this reason we address the difference between the *cell-based* and the *tissue-based* stances" (Soto and Sonnenschein 2011). Soto and Sonnenschein aim at exhibiting the philosophical, more precisely the metaphysical, choices influencing scientific theorizing. What are, then, the *metaphysical basis* of TOFT and SMT? The partisans of TOFT claim that SMT is *reductionist* (Soto and Sonnenschein 2006). More generally, they consider *molecular biology* as the typical reductionist approach (Capp 2012). The concept of *reductionism* is traditionally opposed to *holism* or *organicism* (Marcum 2010). A reductionist approach aims at *analyzing* the complex systems by looking at their fundamental components. On the opposite, an holistic approach considers that the natural phenomena can be explained only by studying them as *a whole*. As a consequence, it is epistemologically useless to consider the smallest scales to study a given object. In biology, *holism* translates into *organicism*, defined as follows by the philosopher J-A.Marcum: "Organicism (…) is an idea utilizing organic unity or a whole to explain biological processes at the level of higher-order entities and their properties rather than simply invoking their elemental composition" (Marcum 2010). This definition is interesting since Marcum presents TOFT as an organicist theory. As a consequence, it is a way to investigate the coherence of this claim. Why do the advocates of TOFT use these concepts? For Soto and Sonnenschein, reductionism,

applied to biology, supposes that the cell is the unit of the organism, and that all the observations made at the tissue level should find an explanation at the cell level. As anti-reductionists, the partisans of TOFT consider themselves as *organicist* (Soto and Sonnenschein 2006). When combining the definition of organicism given previously and the argument of Soto and Sonnenschein, it follows that the *biological process* to explain is cancer, the *high-order entities* are the tissues, and the *elemental composition* are the cells. Is this assimilation of TOFT to a form of *organicism* cogent? In order to answer this question, it is necessary to carefully characterize the concept of *reductionism*. J-A. Marcum defines three types of reductionism (Marcum 2010). *Theoretical reductionism* aims at reducing the terms of a high-level theory to terms belonging to low-level theories. For instance, the biological processes can be described by using concepts borrowed from physics and chemistry. *Ontological reductionism* deals with the description of the elementary components of natural objects or phenomena. Complex phenomena are analyzed by assuming that they are composed of simple elements whose properties explain the general behavior of the system. Applied to biology, ontological reductionism would mean that the observed properties at the organism scale can be explained by the molecular composition of the cells. Finally, *methodological reductionism* is related to the scientific techniques used to decompose the hight-order entities into their low-order elements. In light of these definitions, let us see if TOFT can be considered as an anti-reductionist approach. One can first notice that Soto and Sonnenschein's works rigorously use the same vocabulary as the one used in classical molecular biology. TOFT talks about *cells*, *stroma*, *genes*. It does not consider new terms that we could not be reduced to words referring to elementary components. In other words, the semantic organization of the biological world is exactly the same. Various examples can be found in the articles published by the advocates of TOFT to illustrate this point. The response to the article of Vaux (2011) published by Baker (2011) explicitly uses a typical reductionist vocabulary, such as *intercellular signals* or *oncogenes*. Thus, as regards *theoretical reductionism*, TOFT cannot be said to be anti-reductionnist. Second, the ontology of TOFT is not distinct from the ontology of SMT. The components of the considered biological objects are the same. TOFT gives more importance to tissues, but the tissues are considered as an ensemble of cells, and the cancer remains a cellular disease. An anti-reductionist view would consider the tissue as a whole, without taking into account its cellular/molecular composition. Thus, it does not make sense to argue that TOFT is opposed to reductionism in an ontological reading of the notion. Finally, methodological reductionism is also adopted by the partisans of TOFT. Indeed, they consider the modifications of the *molecular composition* of the stroma when it is exposed to carcinogens. More precisely, the identification of the types of molecules affected is taken into account by Soto and Sonnenschein to build their theory. For instance, they notice in their 2011 article of Soto and Sonnenschein (2011): "Barcellos-Hoff and Ravani irradiated the mammary gland stroma of mice to affect their extracellular matrix composition, cytokine production and receptors involved in cell-to-cell interactions (Barcellos-Hoff and Ravani 2000)". The experimental protocols developed by the partisans of TOFT do consider cells and molecules, hence their methodologically reductionist stance. This rapid analysis

shows that if we consider the classical conception of reductionism given by Marcum (2010), assimilating TOFT to an anti-reductionist approach is not legitimate. If we now follow the definition of reductionism given by the partisans of TOFT, we can also conclude that their argumentation is contradictory. As we already said, they judge as *reductionist* all approaches using the cell as the fundamental unit of the organism (Soto and Sonnenschein 2011). But according to TOFT, cancer is still located in individual cells. In particular, one of the theoretical basis of TOFT deals with the default state of the cell (proliferative or quiescent). This means that the advocates of TOFT *need to* consider that the cell is the fundamental unit of the organism. The reason for this is simple: in TOFT as in SMT, cancer is a cellular disease. More generally, according to TOFT, modifications of the molecular composition of the stroma cause cancer. If we return to a more classical meaning of the concept, this is clearly a reductionist stance. SMT looks into the cell, by considering the structure of the DNA, and TOFT looks outside the cell, by considering the molecular relationships between *each cells* and the stroma. We also have to notice that the partisans of TOFT often accept that genetic mutations have a role in carcinogenesis; they just refuse to consider that mutations are the initiators of the disease (Capp 2012). Thus, it is not obvious that TOFT is an organicist theory. By considering current conceptions of this notion, it appears that the assimilation of TOFT to organicism is not sufficiently justified. It is not relevant in the present state of the debate, and therefore it cannot be used to demonstrate the incompatibility between the two theories.

If SMT and TOFT are metaphysically similar, how can we characterize the different representations of cancer they propose? In particular, if they are metaphysically compatible, are TOFT and SMT biologically incompatible? Our suggestion is that, from a biological perspective, the two theories have to be thought as proposing two distinct, and compatible, *causal pathways* which can initiate and promote carcinogenesis. Both mechanisms are experimentally and clinically relevant (Rosenfeld 2013). When reasoning in term of causal pathways, it is possible to make a case for the compatibility of the two theories, by arguing that both the genes and the stroma can influence carcinogenesis. The actual existence of approaches which conciliate TOFT and SMT is a strong biological argument in support of this view. Indeed, J-A. Marcum notes that the two theories can converge in the frame of *system biology*: "system biology avoids locating causation within a single, hierarchical level, so that the flow of causation is in one direction only - whether bottom-up or top-down. Rather, that approach advocates a flow of causation that is bidirectionally or reciprocal in nature" (Marcum 2010). The notion of hierarchical levels is not easy to use in our case. Considering TOFT as a theory belonging to a higher organizational level than SMT poses the same types of problems we already discussed about the supposed organicism of TOFT. As a consequence, it is not so obvious that TOFT and SMT belongs to distinct organizational levels. Thus, rather than considering a *cellular* and a *tissular* scale, we prefer to use the notions of *interior* and *exterior* of the cell. The notion of bidirectional causation is then still interesting, since it considers that carcinogenesis can be influenced by molecular events taking place *in* the cell, or *outside* the cell. In the frame of system biology, TOFT and SMT are thus not considered as two

irreconcilable approaches. The dynamic reciprocity theory (DRT) of Mina Bisell and coworkers explains how the organization of the stroma has an influence on gene expression and control cell proliferation (Nelson and Bissell 2005). The existence of adhesion proteins joining the intracellular environment to the stroma makes possible the building of a bridge between the genetic and tissular approaches. It is then possible to consider causal relationships between the interior and the exterior of the cell. Insofar as TOFT and SMT describe two compatible causal pathways, they can be integrated in a single approach to explain carcinogenesis. And this integration is of a *higher epistemological value* than SMT or TOFT taken separately.

5 Discussion

The controversy between the two main theories of carcinogenesis (SMT and TOFT) is interesting because it uses three levels of argumentation: experimental, epistemological and metaphysical. We have seen that the experimental data are not sufficient to clearly favor one of the two theories. Each approach can explain some biological facts; but numerous observations are difficult to resolve from either of these viewpoints. To be competitive, the partisans of TOFT build an argumentative strategy based on a purported *incompatibility* of their theory with SMT. They appeal to this purported incompatibility to justify the need to reject one of the two theories altogether, in the same way than in Kuhn's scheme, the incommensurability of two theories justifies abandonning one in favor of the other. Naturally, the reader is strongly invited to keep TOFT and abandon SMT.

To justify this key incompatibility-argument, the partisans of TOFT assimilate the conflict between the two theories to a metaphysical opposition between *holism* and *reductionism*. We showed that this argument is specious, since, it is not clear that TOFT is an organicist theory. It shares its semantics, its ontology and its methodology with SMT. This remark does not mean that TOFT is strictly reductionist, in all the possible meanings of this concept. It just shows that the assertion that *TOFT is an organicist theory* is not coherent with the conception of reductionism and organicism it is based on. This idea is not only applicable to Soto and Sonnenschein's work, since other authors, as Marcum (2010), consider TOFT as an organicist theory without coherent and strong arguments. Yet, as we have shown, the assimilation of TOFT to a strict anti-reductionist approach can lead to a non-justified claim that the two theories are not compatible. Thus, if the defenders of TOFT cannot justify more precisely why TOFT can be considered as an organicist theory, it seems more judicious to fully abandon the frame of the reductionism/organicism opposition.

We also claimed that from a biological point of view, the best refutation of Soto and Sonnenschein's view is the actual existence of approaches which conciliate both theories. We finally proposed that SMT and TOFT should be considered as two distinct, and compatible, causal pathways. We insist on the idea of distinct causal pathways that have to be *integrated* in order to build a more accurate and satisfying description of carcinogenesis. This view is closed to the ideas exposed by Sandra D. Mitchell about biological complexity (Mitchell 2002, 2004). The author defends the

idea of an integration of the different causal pathways describing complex biological objects into a unified explanation. According to Mitchell, the idealized character of biological models make necessary the emergence of *partial* theories, considering only *one* causal pathway. Often, the compatibility of these theories stems from the possibility of a theoretical integration. We have seen that this integration can be achieved in the frame of system biology, which considers the multiple causal relationships linking the cell, the stroma, and the development of cancers. We can notice that such causal relationships make carcinogenesis a strongly non-linear phenomenon. As a consequence, the development of integrative approaches can depend on the ability to build global models of carcinogenesis. Progress in computational modeling in biology favors the development of these approaches. The existence of these new tools for investigating carcinogenesis is a strong argument against the sterile postulate of incompatibility.

Finally, let us recall that this claim for an integration of TOFT and SMT is not new (Marcum 2010; Rosenfeld 2013; Coffman 2005). However, our original contribution is the theoretical justification showing the lack of relevance of the idea of a fundamental incompatibility between the two theories. Whereas the previous discussions about the possibility of an integration of TOFT and SMT do not question the relevance of the reductionism/organicism opposition in the field of carcinogenesis, we suggest that in the present state of the debate, this frame should be abandoned.

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