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Are the Somatic Mutation and Tissue Organization Field Theories of Carcinogenesis Incompatible?

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ABSTRACT: Two drastically different approaches to understanding the forces driving carcinogenesis have crystallized through years of research. These are the somatic mutation theory (SMT) and the tissue organization field theory (TOFT). The essence of SMT is that cancer is derived from a single somatic cell that has successively accumulated multiple DNA mutations, and that those mutations occur on genes which control cell proliferation and cell cycle. Thus, according to SMT, neoplastic lesions are the results of DNA-level events. Conversely, according to TOFT, carcinogenesis is primarily a problem of tissue organization: carcinogenic agents destroy the normal tissue architecture thus disrupting cell-to-cell signaling and compromising genomic integrity. Hence, in TOFT the DNA mutations are the effect, and not the cause, of the tissue-level events. Cardinal importance of successful resolution of the TOFT versus SMT controversy dwells in the fact that, according to SMT, cancer is a unidirectional and mostly irreversible disease; whereas, according to TOFT, it is curable and reversible. In this paper, our goal is to outline a plausible scenario in which TOFT and SMT can be reconciled using the framework and concepts of the self-organized criticality (SOC), the principle proven to be extremely fruitful in a wide range of disciplines pertaining to natural phenomena, to biological communities, to large-scale social developments, to technological networks, and to many other subjects of research.

KEYWORDS: self-organized criticality, somatic mutations, carcinogenesis, avalanches, quorum sensing, swarm intelligence

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Introduction

Two drastically different approaches to understanding the driving forces behind cancer onset and proliferation have crystallized through years of research. These are the somatic mutation theory (SMT) and the tissue organization field theory (TOFT). The essence of SMT is that cancer is derived from a single somatic cell which has successively accumulated multiple DNA mutations, and that those mutations occur on genes which control cell proliferation and cell cycle. Thus, according to SMT the neoplastic lesions that destroy normal tissue architecture are the results of DNA-level events. Conversely, according to TOFT, carcinogenesis is primarily a problem of tissue organization: carcinogenic agents (eg, environmental chemicals, inflammation, viruses) destroy the normal tissue architecture thus disrupting cell-to-cell signaling and compromising genomic integrity. Hence, in TOFT the DNA mutations are the effect, and not the cause, of the tissue-level events.[1]

The SMT and TOFT have a long history of development, perhaps under the disguise of constantly evolving terminologies. The best source of relevant information is the book by Sonneschein and Soto.[2] A concise, yet comprehensive, overview of this history can also be found in the review by Baker.[3] Arguments in favor of both TOFT and SMT are numerous and strong, as seen, for example, from two papers[4,5] recently published next to each other. At the same time, a large grey zone of biological facts and clinical cases exists which poses the questions that are difficult to resolve from either of these viewpoints.[6] Essentially, for a long time the theories conceptually close to SMT and TOFT were considered as two different facets (along with many others) of the complex phenomenon of carcinogenesis. It is a comparatively new

development that SMT and TOFT began to be regarded as irreconcilable alternatives. Thus, according to Sonnenschein and Soto,[7] TOFT and SMT "belong to distinct levels of biological complexity and therefore, are incompatible, as are their philosophical stances (reductionism versus organicism)." Indeed, the cornerstone of SMT is the notion that carcinogenesis is triggered by a single aberrant cell which happened to acquire multiple DNA mutations, and that these mutations predominantly damage the genes responsible for the cell cycle and apoptosis.[8] Frequently observed monoclonality of the initial cancer cell population is an important evidence supporting SMT. In particular, as observed by Nowell, "cytogenetic studies have demonstrated that in many primary tumors all cells show the same abnormal karyotype; the immunoglobulin produced by plasma cell tumors has in almost every case the homogeneity characteristic of a single clone."[9] As an ultimate manifestation of this paradigm, direct evidence of a single catastrophic event triggering carcinogenesis has been presented by Stephens et al.[10] The authors report: "The model to explain the distinctive genomic structures described here is that the overwhelming majority of rearrangements occur in a single catastrophic event. In this scenario, the chromosome or chromosomal region shatters into tens to hundreds of pieces, some (but not all) of which are then stitched together by the DNA repair machinery in a mosaic patchwork of genomic fragments ... A cell suffering tens to hundreds of DNA breaks in a single cataclysmic event would be expected to undergo apoptosis. That a cell can survive such an insult and progress to become cancerous suggests that the extensive remodeling of the genome may confer significant selective advantage to that clone."

In direct opposition to these views, TOFT depicts carcinogenesis as general deterioration of the tissue microenvironment due to extracellular causes. This deterioration hinders normal cell-to-cell signaling thus making normal functioning of the intracellular machinery impossible and eventually leading it to the breaking point. In such a scenario, the deleterious mutations should be scattered all over the genome randomly and incoherently with little chance for clonal homogeneity. According to SMT, cancer progression is a unidirectional and mostly irreversible process; the disease cannot be cured unless the entire tumor mass is surgically removed, radiationally killed, or deprived of its aggressive nature by carefully targeted chemotherapeutic agent. Paramount importance of TOFT for cancer biology, for the practice of clinical oncology and for cancer prevention, dwells in the fact that according to this view carcinogenesis is not a unidirectional process; rather, it is curable and reversible.[11]

In this paper, we do not take sides in this clash of seemingly irreconcilable views. Our goal here is to outline a plausible scenario in which a single event, insignificant on its own, may trigger a system-wide catastrophic restructuring. Such a scenario may be envisioned and conceptualized within the framework of the so called self-organized criticality (SOC). Self-organized critical phenomena are wide-spread in nature and society. For example, a large-scale devastating forest fire may be sparked by a single cigarette butt, but abundant availability of flammable dry wood is the prerequisite. A minor shock to overstressed tectonic plates may destroy their precarious equilibrium and cause a large-scale earthquake followed by a tsunami. A single micron-size dust particle dropped into a vessel with overcooled liquid may cause rapid crystallization of the entire mass of liquid. In a society overburdened by internal strife and misery, a charismatic self-motivated leader may grab attention of a disoriented crowd and become a seed for rapid transition to new modalities of existence.[12,13] All these dissimilar phenomena have one fundamental feature in common: the system resides in a metastable state and its collapse may be triggered by a small-scale event insignificant on its own.

In what follows, we attempt to amass systemic arguments and known biological facts in favor of the proposed scenario.

Brief Overview of Self-Organized Criticality

SOC is an avalanche-like system-wide transformation which rapidly moves a system into a new state.[14–16] A popular metaphor for SOC is the sandpile paradigm. If additional sand grains are randomly added to a sand pile then inevitably an instance will occur when local steepness of the slope surpasses a certain critical threshold thus causing local failure of structural stability. The excess of material will cascade into adjacent areas of the pile causing their failure as well. Thus an avalanche will occur, shifting the entire sandpile into a new stable state. What is fundamentally important in this process is that a random local event quickly propagates through the entire system thus establishing long-range correlations within the system. A simple cellular automaton describes the sandpile paradigm in more refined mathematical terms. Suppose that there exists a two-dimensional lattice of cells in which the state of each cell is characterized by a time-dependent load, $\upsilon_{ij}(t)$. Suppose also that there exists a limiting capacity of each cell, $\bar{\upsilon}_{ij}$, and every time when $\upsilon_{ij}(t) > \bar{\upsilon}_{ij}$, the excess of load, that is, $\upsilon_{ij}(t) - \bar{\upsilon}_{ij}$, is randomly redistributed among the neighboring sites. After one step of random redistribution, one or more neighboring sites may become overloaded, thus causing the domino effect of subsequent instabilities resulting in an avalanche. The actual meaning of the quantity symbolized by the word *load* may vary. In particular, it may represent a certain amount of information; in this case, occurrence of the system-wide coherence may be interpreted as *rapid information transfer* (recall rapid rumor propagation in a community anticipating some breaking news). Obviously, the rules of the game would remain essentially the same if, instead of a lattice of the cells, one considers a *network* of interacting units with an arbitrary topology. It is of crucial importance to realize that the network-wide information transfer and coherent restructuring is not a result of long-range exchange of signals, neither is it a result of collective thinking or following the orders of some sort of command center. It is the result

solely of local stimulus-response interactions between the neighbors. The role of SOC in rapid system-wide restructuring has been studied in many works (see [17–19] and references therein). Slight variation in the rules of updating may drastically change the overall dynamics of the system. For example, in the model[15] proposed by this author, the loads, per reaching critical capacity, are randomly redistributed not only among the neighbors (as in the sandpile paradigm) but also among all members of the community. This simple modification of rules leads to a fundamentally different behavior of the system; that is, to the excitation of self-organized self-sustained oscillations. In physics, avalanches are known under the name *phase transition*, with the subcritical states preceding the transition being called *metastable*. The transition itself may be triggered by a minor event with little significance of its own; due to this insignificance the phase transition may appear to be spontaneous. However, spontaneity does not mean that there is no reason for phase transition; the fundamental reason is that the system resides in a subcritical state and is ripe for collapse. A brief list of examples of SOC from other disciplines include earthquakes, wild fires, landslides, revolutions, epidemics, crowd stampedes, stock market crashes, rumor propagation, bird flock self-organization, snow avalanches, and, of course, sandpile avalanches and dune formation. A common feature among all these diverse examples is that prior to a catastrophic event, the system resides in subcritical state and is ripe for restructuring. After the catastrophe, the system moves itself into a new stable state, but this state is again subcritical. The long-term dynamics of such systems represents various patterns of intermittency. As to the period of transition between the sequential critical states, an avalanche itself is an essentially random process; in this sense the temporary stability is often said to exist *on the edge of chaos*. A fundamental property of SOC is that a minor event may trigger a large-scale system-wide response, thus serving as a natural amplifier of weak and insignificant signals.

Self-Organized Criticality in Molecular Biology

Genetic regulatory network (GRN) in an individual cell is an excellent example of a system permanently existing on the edge of chaos. This aspect of intracellular regulatory dynamics has been extensively covered in the literature,[20–22] including publications by this author.[15,23–26] A brief synopsis of relevant ideas is as follows. Each transcription event, ie, synthesis of a single mRNA molecule, requires participation of a large number of transcription factors (TFs) which essentially are the proteins expressed by other genes. In turn, these supporting proteins cannot come into existence unless their parent genes have complete teams of their own TFs coming from yet another set of genes. This tight interdependence of genes (often metaphorically referred to as *gene-to-gene interactions*) creates the situation when each gene may be expressed only with the support of many other genes, essentially of the entire GRN. The situation may be likened to a large number of assembly lines working in parallel and each requiring a large number of parts produced by other assembly lines. Ideally, the system can only work in a perfectly synchronized manner, with each of thousands of parts being produced and delivered where needed in a timely manner. If, however, at least one part fails to arrive in time to its destination, the corresponding assembly line then comes to a stop, thus triggering the domino effect of secondary failures and ultimately driving the entire system to a complete halt. This domino effect is similar to what earlier in this paper has been called an avalanche. The work may only be resumed by starting everything anew, again in a perfectly synchronized manner. In mathematical terms, the question which is discussed here is the question of dynamic stability. If a multidimensional dynamical system consists of many tightly interacting units then the probability that such a system may reside in a steady state equilibrium is negligibly small.[27] The only mode of motion conceivable in such a system is sporadic jumping from one instance of perfect synchronization to another. A well-documented and frequently occurring phenomenon of burstiness is a vivid manifestation of this sporadicity.[28–31] The concept of stochastic cooperativity introduced by this author[32] helps to conceptualize this important phenomenon.

A deep insight into critical dynamics of GRN has been given by Balleza, et al.[22] Using a reasonably well-established model of Boolean network for representation of the GRN, the authors demonstrate "existence of a dynamical phase transition from ordered to chaotic dynamics." Furthermore, using microarray data gleaned from the organisms belonging to four distinct kingdoms (*Saccharomyces cerevisiae, Escherichia coli, Bacillus subtilis, Drosophila melanogaster, Arabidopsis thaliana*), they also demonstrate that critical dynamics of their GRNs is largely similar to that envisioned by the Boolean model. Based on empirical data and simulation experiments, Balleza et al.[22] also conclude that "critical behavior observed in the dynamics of the genetic networks of the organisms under study is mainly produced by the network architecture rather than by the specific nature of the regulatory functions." This conjecture is significant. It essentially states that studying the network topology, that is, the arrangements of the links between its nodes, is of superior importance as compared to studying the specific biochemical details of the interactions symbolized by these links.

GRN is just one example of a biological system which permanently resides in subcritical regime on the edge of chaos. There is a well-rooted paradigm in theoretical biology that the phenomenon of life as a whole, from the level of cells through the level of populations and up to the level of society, is a perpetual existence on the verge of collapse.[12,33–36] Comparatively simple and universal forces driving the living systems towards critical conditions are always present behind the scenes in all SOC phenomena. In very general terms, a hallmark of living entities is their ability to replicate and proliferate themselves. In a community of such entities, unstoppable proliferation will inevitably drive the

community towards exhaustion of common resources, whatever these resources are, thus bringing the populations to the verge of extinction. Nice illustrations of the basic mechanisms leading to SOC in living systems has been given by Adami.[37]

SOC plays an important role in DNA damage and transition of cellular machinery into chaotic state. A meticulously well-studied example of this kind has been given in the work by Yarosh[38] which focused on the DNA damage induced by the UV radiation. According to this work, the sequence of molecular events in such a process unfolds as follows: the first cellular factor to sustain the damage is the RNA Polymerase II during the transcription of an active gene; this damage leads to a stalled transcription fork. The stalled fork triggers DNA repair mechanisms by attracting a large number of proteins which, in turn, allosterically modify binding affinities of many other proteins. It may happen that the damage occurs in the so called "hub" proteins (such as p53 protein)[38] which are capable of modifying a large number of vital cellular functions simultaneously. A subtle balance always exists between the rates of damage and repair. Up to a certain level of mutagenic load, the repair mechanisms are capable of containing damage, thus maintaining a generally healthy cell population. However, the *last straw* effect may also occur when the cell, after an insult, remains unrepaired yet undestroyed, thus giving rise to a genetically aberrant sub-population. This last straw event is analogous to the last grain of sand in the sandpile avalanche because it fires up multiple, very complex, and mostly irreversible pathways. Such a massive complex response to a seemingly minor event is a hallmark of SOC. It would be an obvious misjudgment to regard any particular minor event as a cause of the system's collapse. Rather, one may expect that a mutationally overloaded system would collapse anyway, whatever a minor event actually happens to be the trigger.

Another example in which SOC plays an important role is the autoimmune disease known as *systemic lupus erythematosus* (SLE)[39]; much of what is said with respect to SLE is also applicable to autoimmune diseases in general.[40] The authors write: "We therefore conclude that systemic autoimmunity necessarily takes place when host's immune system is overstimulated by external disturbance, ie, repeated exposure to antigen, to the levels that surpass system's self-organized criticality, and propose here 'self-organized criticality theory' explaining the cause of autoimmunity." Recent developments in cancer research reveal deep connections between autoimmunity and carcinogenesis—both disturbing and promising. Thus, the authors of a detailed review[41] indicate: "Complex relationship between autoimmunity and cancer has been reported in numerous studies over the past years, based on the assumption that autoimmune disease and malignancies share several common features. Clinical observations suggest that autoimmunity and malignancy are linked in a bidirectional way as clinical features resembling autoimmune disease are frequently encountered in paraneoplastic syndromes." In the context of SOC, these conclusions may have quite an ominous connotation: overstressing the immune system beyond a certain breaking point may cause a disproportionally massive response in the form of a cluster of autoimmune diseases, including SLE and cancer.

SOC is a fundamental, all-pervading principle manifesting itself in a large variety of forms throughout all the levels and types of biological organization. SOC is a core mechanism governing spontaneous transition of an organism or biomolecular system towards higher levels of complexity. An excellent discussion of this aspect of SOC may be found in the paper by Suki,[42] in which the author argues that "sudden and unexpected improvement in the functionality of an organism is enabled by a phase transition in the network structure associated with that function." Major transitions of life include, but are not limited to, emergence of living matter, eukaryotic cells, photosynthesis, sex, multicellularity, vision, consciousness, language, culture, and society. This view of avalanche-like qualitative leaps is somewhat alternative to the vision of evolution as a slow accumulation of beneficial traits through the generations of an organism. Rather, they represent the patterns of punctuated evolution, as proposed in the seminal paper by Gould and Eldredge.[43] According to the views expressed by Suki,[42] when the link density in a network increases, whatever the network is or schematically represents, a critical state will inevitably occur beyond which a new property of the network would spontaneously emerge. This property would belong to a higher level of complexity and brings about new functionality. Transplanted into the context of carcinogenesis, one may hypothesize that up to a certain critical level of population, the aberrant cells behave quasi-independently of each other and as a whole do not constitute a community of tightly interdependent entities. At this stage, aberrant cells fight for their existence individually, without support of other cells. However, when the link density crosses the critical threshold, the network of aberrant cells collapses into a coherent self-organized mode, and subsequently behaves as a community sharing the common purpose of survival.

Revisiting the Concept of Default States

As pointed out by Sonnenschein and Soto,[7] the SMT versus TOFT dichotomy may be boiled down to the following core question: What is the *default* state of the cell, proliferation, or quiescence? According to SMT, cancer cells develop the ability to defy the mechanisms of apoptosis, to outtrick the immune system responsible for their elimination, and as a result, to obtain exclusive capabilities to survive, to proliferate, and to transfer deleterious mutations to progeny. Thus, in SMT, proliferation is claimed to be a distinctive feature and the default state of cancer cells; in contrast, the default state of normal cells is assumed to be quiescence. Conversely, according to TOFT, there is no such thing as cancer cells. This is because cancer is the tissue level disease, and proliferation is the default state of any cell.

The authors[7] indicate: "Based on an evolutionary perspective and on our experience using a variety of cell culture models and their animal counterparts, we favor the concept that the default state of cells in metazoa, like those of unicellular organisms and metaphyta, is proliferation. In a recent revisiting of the subject, we became aware that at the end of the 19th century, the famed pathologist H. Ribbert postulated that cancer cells, freed from the restraint of tissue structure, would express their constitutive property to proliferate." This conceptual view was further elaborated as follows: "Implicitly, the SMT also adopts the premise that, unlike in unicellular organisms, quiescence is the default state of cells in metazoa. In effect, such claims ignore the fundamental fact that cancer can only arise in metazoa in the context of complex and highly differentiated tissue structures."[4] And further: "Switching premises regarding the default state of cells from quiescence, as adopted by the proponents of the SMT, to proliferation, as stated by the TOFT, qualifies as a *paradigmatic change* in both a narrow (limited to the field of carcinogenesis) and a broad sense because it proposes incorporating a novel evolutionary perspective into the field of carcinogenesis and in its relationship with that of biology at large." (italicized by SR)[4]

Due to the extraordinary importance emphasized above of the concept of default state for cancer biology and biology at large, it seems worthwhile to explore this concept in more detail. To the best of the author's knowledge, there has been no attempt in the literature to provide a more or less crisp definition of the concept of default state. Therefore, when applying this concept one should mostly rely on one's own intuition, as well as on the analogies and metaphors borrowed from other domains of science and social experience. On the other hand, since the concept of default state has been placed in the center of argument of paradigmatic proportion, it is vitally important to reach some sort of consensus regarding the meaning of this concept.

At first glance, it may be thought that the words default state are somewhat equivalent to *the natural or naturally-predisposed state*. Although it sounds approximately right, the drawback is that there is not much of an illuminating potential in such a definition; this is because everything in the nature is, of course, natural. A little more specificity may be found in Huang,[44] where the default state is equated to the state that "needs not to be actively maintained." This definition is fairly ambiguous; it provokes more questions than it is able to resolve. Indeed, one conceivable way the aforementioned active maintenance may be realized is through the interactions with other cells and extracellular matrix; hence, it could be said that the community of cells is the entity taking responsibility for the individual cell's maintenance. Such definition, however, lacks specificity; under this definition, there is no difference between the default state and any other arbitrary non-default state. An alternative logical possibility is that active maintenance is governed by some external *layer of control or by supervisory authority*. Obviously, this possibility should be ruled out in the *in vivo* biology; however, active maintenance by external forces is indeed conceivable and always occurs in the *in vitro* biology. Adherence to such definition would automatically mean that the very definitions of the default states in the *in vivo* and *in vitro* biology are not consistent with each other. Therefore, it would not be logically justifiable to observe the default states in the laboratory and then to extrapolate the observations towards in vivo conditions.

The originators of TOFT propose the following definition of the default state: "By default state we mean the state in which the cells are found when they are freed from any active control."[11] The reservations expressed in the previous paragraph are mostly applicable to this definition as well. With this definition, the crux of the issue is what should be regarded as an "active control?" It is not just a terminological hair-splitting; a fundamental question is at stake: How is the cell expected to behave when it is allowed to act on its own in accordance with its natural propensity? Implicitly, existence of such a natural propensity assumes that the cell is a self-sustained and self-motivated organism capable of living on its own and independently of the society it belongs to. *In vivo*, the active control mentioned above can be only thought of as the control coming from other cells in the tissue. Freedom from any active control (stipulated by the above cited definition)[11] is a hypothetical situation in which the cell lives outside its native environment but nevertheless retains the same intrinsic properties that it would have when being tightly embedded in it. Essentially, such a notion equates a cell with a unicellular organism whose "constitutive properties," according to the above cited definition by H. Ribbert, are best seen if the cell is freed from any active control of other cells.

We would like to re-emphasize that the discussion here is about determining what the definition of the concept of default state is, rather than about what the cells actually do while residing in their hypothesized default states. As seen from the above considerations, a non-trivial (ie, bearing some reasonable level of specificity) and yet logically self-consistent definition of the concept of the default state is elusive. On the other hand, ample experimental evidence is available which casts a shadow of doubt on the very existence of the default states. As demonstrated in many works, the phenotypic traits of individual cells are shaped by interactions within their respective communities.[45–50] Therefore, the default states of the cells "freed from the restraints of tissue structure" may not be identical, or even similar, to those that are densely packed and immobilized in tissue. Numerous examples of phenotypic dependencies between the cellular states and specific circumstances in which the cells are functioning come from microbiology. Thus, it has been shown in a landmark work[47] that bacterial communities in biofilms (closely mimicking somatic cells in the tissue) are capable of maintaining self-identity, purposeful alterations of the colony structure, and recognition and identification of other colonies. This is an amazing example demonstrating that unicellular organisms are capable

of modifying their phenotypic traits (default states) to the extent that make them capable of distinguishing between allies and enemies, and mounting collective defense against the genotypically identical rivals. Examples of this kind are numerous; they indicate that the default states of individual cells are largely shaped by their roles and positions within the community. Essentially, all this means that the concept of default state is an abstract idealization and simplification with limited applicability to real states of the cells, either in tissue or in culture.

In a larger context, the concept of default state is not quite satisfactory from a purely logical perspective. It is not self-evident why such an entity as the cell deserves the honor to have some sovereign default state, but a community of the cells, as a whole, would not. Astounding coherence observed between all the elementary processes on various levels of biological organization allows one to see a community of cells as a superorganism or even as a separate organ,[51,52] and to talk about its "defensive tactics."[53] The most fundamental property of a superorganism is the shared purpose of its existence.[54] Therefore, if we continue to ascribe specific default states to various biological entities, it seems legitimate to ask: What is the default state of a superorganism? This line of troubling questions may be extended towards internal structure of the cell. Patterns of highly organized behavior are observed in intra-cellular processes.[55] After having postulated existence of some natural default state of the cell, should we now continue inward by ascribing some default states to individual genes, to individual mitochondrions, to individual RNA Polymerases, or to individual proteins? If one starts making such *a priori* statements at some hierarchical level and then logically extends this process to adjacent hierarchical levels, then ultimately the entire system of knowledge will be transformed into the collection of *a priori* postulated descriptors of the default states. Hence, no scientific inquiry would be necessary if all the conceivable default states and behaviors are appropriately postulated and cataloged *a priori*. All this is to say that assumptions regarding the very existence of the default states may be a shaky basis for erecting a massive edifice of the theory of carcinogenesis.

It is our view that the roots of logical difficulties in giving a crisp definition to the concept of default state stem from the fact that the cells possess a rich gamut of functions widely varying in the degree of their autonomy. Some of these functions are fully automatic and work in the same way under any circumstances, whether within or outside the network of cells. Others depend on the inputs from other cells and extracellular sources; these functions retain a high degree of autonomy but are modifiable by external forces. Still other functions are completely dependent on interactions with other cells; these functions are unthinkable if the cell is freed from any active control (as stipulated by the definition cited above). All these numerous properties and behaviors, separately or in combination, form an intricate mosaic of possible default states. We conclude this section with the conjecture that the concept of default state may receive a specific meaning only within a specific operational context. Therefore, the question "what is the default state of the cell?" does not make much sense out of the context of a dynamic environment to which it belongs. The tendency to proliferate, or to be quiescent, or to follow a more elaborate patterns of phenotypic behavior would strongly depend on the specific stimulus-response rules imposed by the community of cells.

What do the Words Communications and Architecture Mean in the Context of Carcinogenesis?

Another persistent motif in the TOFT discourse is that carcinogenic agents, whatever they are, destroy the normal tissue architecture thus disrupting the intercellular communications and depriving the intracellular machinery of necessary resources for seamless functioning. For example, Sonneschein and Soto claim: "The second premise [of TOFT] is that carcinogenesis are defects of tissue architecture. Specifically, the targets of carcinogens would be all the morphogenetic fields comprising interacting tissues. In this context, physical, chemical, and biological carcinogens qualify as disruptors of tissue architecture."[1] This general characterization is echoed and further detailed in many other works. For example, as indicated by Potter: "metaplasias and cancer are characterized, at the earliest stages, by disruption of the standing-wave templates, which leads to a shift in phenotypes and a change in tissue microarchitecture."[56] Obviously, the word *architecture* used in this context is a metaphor borrowed from a completely different domain of experience. For reference purposes, here is what the Merriam-Webster dictionary tells us regarding the meanings of the word architecture: i) the art or science of building; specifically: the art or practice of designing and building structures and especially habitable ones; ii) formation or construction resulting from or as if from a conscious act; iii) a unifying or coherent form or structure; iv) architectural product or work; and v) a method or style of building. Apparently, definition iii) provides the meaning which best fits into the biological context. Basically, structural integrity of the tissue is the key element brought about by invoking the metaphor of architecture.

There is another, distinctly different aspect of the TOFT: cell-to-cell communication. We find in Soto and Sonnenschein: "Altered communication among cells is at the core of the TOFT."[11] In the above-mentioned review by Baker,[3] importance of cell-to-cell communications for the entire TOFT paradigm is summarized as follows: "The tissue organization field theory says that cancers arise from a disruption of cell communication needed to maintain normal tissue architecture." Although the general intuitive meaning of the above statements seems to be quite clear, it is nevertheless fairly obvious that the concept of *communication* transplanted into the bimolecular context is a metaphor that should not be taken too literally and pushed too far along the ways of analogy.

Taken literally, the disruption of communications cannot be an immediate cause of ruining the architecture. Using an analogy, when the internet connection in one's home is down, the home itself remains standing and does not immediately collapse. It is useful again to check with the Merriam-Webster dictionary regarding the authentic meaning of the word communication: "communication is a process by which information is exchanged between individuals through a common system of symbols, signs, or behavior." Information, in turn, is a coded message transmitted from an entity called transmitter (T) to an entity called receiver (R) using a language common to both T and R. Fundamentally, neither the language nor the algorithms of coding and decoding of its symbols are the creations of T or R; they should be in existence prior to the process of information transfer. This is a big difference with molecular communications where the T, the R, and the language they use belong to the same realm on organic molecules and biochemical reactions. It should also be noted that information transfer by itself is not sufficient to cause any action; some sort of mechanism is still required for reading information and transforming it into mechanical or chemical changes. The point we are making here is that a fair amount of imagination is required in order to envision the parallels between the information transfer and cascading biochemical reactions constituting the cells' life. Such parallels are helpful but not reliable in creating a logically self-consistent theory. The metaphor of cell-to-cell communication implicitly elevates the cells to the status of self-motivated individuals each possessing some knowledge and communicating with each other in the business of maintaining the tissue architecture. All these metaphorical constructions are nothing else than the crutches for the human mind to cope with biomolecular complexity and to somehow succinctly conceptualize a big picture of myriads of biochemical processes inside the cells. In summary, it does not seem sufficient just to say that the disruption of cell-to-cell communication and damage to tissue architecture are the primary causes of carcinogenesis.

Precancerous Tissue is the System in Critical State on the Verge of Collapse

There are great many of biochemical contexts and structural characterizations in which the evolution of tissue, from a healthy state to a precancerous state and further to tumorigenesis, may be described and analyzed. In particular, chronic systemic inflammation has been widely recognized to be among the leading factors in progression of healthy tissue towards precancerous and cancerous lesions. The specific mechanisms of such progression include sustained cell proliferation in an environment rich in inflammatory cells and molecular agents causing DNA damage.[57] As observed by Lee et al.: "Excessive and pathologic inflammation causes DNA damage, genomic instability, epigenetic dysregulation, and alteration of intracellular signaling, all of which are involved in neoplastic transformation."[58] It is important to realize that inflammation-triggered carcinogenesis cannot be reduced to just cell proliferation and conquering new tissue territories (as simple ecological analogies would suggest). A number of complex molecular mediators facilitate proliferation of genomic damage, among which an important role belongs to inflammasomes, ie, the multi-protein complexes that mediate immune response.[59] As seen from the above description, there is a striking similarity between the pictures of inflammatory damage proliferation through tissue and flame propagation through dry forest (as the very word *inflammation* would suggest.)

Another fundamental aspect of carcinogenesis is the DNA methylation. In normal tissue, gene methylation is mostly localized in the coding region whereas the promoter region remains mostly unmethylated. A different pattern is observed in neoplasia: the genome-wide hypomethylation is accompanied by localized hypermethylation. Evidence suggests that methylation is an important factor in carcinogenesis since genome-wide hypomethylation can trigger the chromosome instability and increase the mutation rates.[60] Laird et al observed that "DNA methylation changes in cancer cells are not mere by-products of malignant transformation, but can play an instrumental role in the cancer process. It seems clear that DNA methylation plays a variety of roles in different cancer types and probably at different stages of oncogenesis."[61] Generally, abnormal patterns of methylation signify elevated cancer risk due to heightened susceptibility to cancer cell proliferation.

According to Vendramini-Costa and Carvalho,[62] tumor initiation involves irreversible changes in DNA through activation of oncogenes or inactivation of tumor suppressor genes. Further development leads mutated cells to expansion through increased proliferation and suppression of cell death. In the process of invasion of adjacent tissues cancer cells may accumulate other mutations, thus exacerbating their phenotype. Again, the process is quite similar to the forest fire propagation, which accumulates additional strength while invading new territories.

As briefly touched upon above, disruption of cell-to-cell communication is an important aspect characterizing precancerous tissue.[51] In TOFT, this disruption is seen as a central component of a bigger process of tissue disorganization. But there is more. The viewpoint being advanced in the previous paper by this author[63] is that a community of cells is not simply a collection of units dwelling within certain architectural structures. This is indeed a living community possessing the emergent property of *swarm intelligence*. (By definition,[64] "swarm intelligence is the organized behavior of large communities without global organizer and without mapping the global behavior onto the cognitive/behavioral abilities of the individual members of the community.") With the destruction of signaling pathways, not only the normal regulation of individual cellular processes is damaged, but also a blow is dealt, so to speak, to the *mental* capabilities of the

community as a whole. Its collective memory is wiped out or distorted, customary division of labor between subpopulations is shifted towards aberrant modalities, and community-wide self-defense mechanisms are weakened or broken. These processes in turn cause a shift in expression profiles and metabolic dynamics, eventually penetrating to the level of DNA and causing multiple mutations. An important aspect of swarm intelligence is the faculty of *quorum sensing* (QS). There is a growing consensus in the cancer research community regarding the fundamental importance of disruption of QS in cancer onset and proliferation. Agur et al.[65] provide a brief review of relevant biological facts and propose a mathematical model of QS boiled down to its simplest mechanistic elements. They conclude "that cancer initiation is driven by disruption of the QS mechanism, either by genetic mutations, complying with the current notion of cancer evolution, or purely by the environment, genetic mutations being only a side-effect of excessive proliferation." Disruption of QS aggravates weaknesses of the tissue defenses thus moving the system closer to the verge of collapse.

As seen from the above discussion, the mechanisms of tumor initiation play a prominent role in carcinogenesis, and a single catastrophic event indeed can make a fundamental impact on all subsequent events. However, it goes without saying that not every event that may be seen as catastrophic on the level of individual cell would necessarily lead to carcinogenesis. Vast majority of those events would fade and disappear without traces. This is because the immune system remains on guard of tissue homeostasis. When tissue homeostasis is perturbed, sentinel macrophages and mast cells release cytokines, chemokines, reactive oxygen species (ROS), and other bioactive mediators that induce mobilization of additional leukocytes.[66] This means that the mutant cell capable of starting the domino-effect of subsequent failures should be able to overcome the tissue's natural defenses; this may happen only if the tissue is already preconditioned for failure and resides on the verge of systemic collapse.

Conclusion: Self-Organized Criticality in Carcinogenesis

In the section above, we attempted to provide just a glimpse of extremely complex and tangled transition of healthy tissue towards precancerous state. Obviously, even a complete knowledge of each and every process contributing to this transition does not automatically lead to understanding the process as a whole. Resorting again to the sandpile analogy, it would be as difficult as understanding the phenomenon of avalanche from observations of each and every sand grain trajectory. This is why systemic approaches are not simply helpful, they are absolutely necessary and unavoidable for synthesizing existing biomolecular knowledge into a coherent picture of carcinogenesis. The SOC paradigm is one such approach.

From the considerations presented in this paper, it follows that neither a single catastrophic event nor a persistent damage to the tissue architecture and to the cell-to-cell communications, taken separately, are sufficient for triggering carcinogenesis. Rather, they represent various inseparable faces of the same process. The carcinogenesis scenario outlined above is characteristic for the manifestations of SOC: from the systemic point of view, it is quite analogous to wild forest fires, to economic collapses, to electric grid blackouts, to rumor propagations, and to many other phenomena uniformly conceptualized by the theory of SOC. Within the SOC scenario, TOFT and SMT do not contradict each other but come into confluence and complement each other in a single unified theory of carcinogenesis.

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Author Contributions

Conceived the concept: SR. Wrote the first draft of the manuscript: SR. Made critical revisions and approved final version: SR.

DISCLOSURES AND ETHICS

As a requirement of publication the author has provided signed confirmation of compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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