QUADERNO

IL CANCRO E LA SUA COMPLESSITÀ: SPIEGARE E CURARE IL CANCRO: TEORIE SULLA CARCINOGENESI E APPROCCI TERAPEUTICI

CANCER AND ITS COMPLEXITY: EXPLAINING AND CURING CANCER: THEORIES ON CARCINOGENESIS AND THERAPEUTIC APPROACHES

Paradoxes in somatic mutation theory of carcinogenesis

Paradossi nella teoria carcinogenica basata sulle mutazioni somatiche

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The Somatic Mutation Theory of carcinogenesis encompasses significant inconsistencies and, as now admitted by its own supporters, can hardly explain the emergence of tissue-based processes, like cancer. The increasingly burden of unexplained paradoxes and shortfalls is driving the current carcinogenesis theory toward a blind alley. Ignoring these paradoxes is unsustainable. By avoiding facing these conundrums the scientific community is depriving itself of the opportunity to achieve real progress in this important biomedical field. To remedy this situation, cancer research should be reframed by embracing new theoretical perspectives, taking the cells-microenvironment interplay as the privileged etiopathogenic level of observation, and by assuming radically different premises as well as new methodological settings. Valuable hints along that direction have been provided during last decades by alternatives theories such as theTissue Organization Field Theory, according to which cancer arises as a consequence of altered cross-talk among cells and their microenvironment, involving both biophysical and molecular cues. This novel approach may effectively solve paradoxes and puzzling observations in carcinogenesis studies.

Key words: Tumor-microenvironment, TOFT, cancer reversion, mutations, systems biology

La teoria carcinogenica della Mutazione Somatica del Cancro è andata accumulando incongruenze e contraddizioni, oggi apertamente ammesse anche dai suoi sostenitori, che la rendono inadeguata a spiegare l'emergere di fenomeni complessi come il cancro. Ignorare questi paradossi è insostenibile, e il farlo sta portando la ricerca oncologica in un vicolo cieco. Ancor peggio, se queste evidenze continuassero ad essere marginalizzate dal dibattito scientifico, la comunità scientifica si priverebbe della opportunità di conseguire un autentico progresso. Per superare quest'impasse occorre abbracciare nuove prospettive teoretiche, prendendo come livello privilegiato di osservazione dei fenomeni biologici quello rappresentato dal tessuto, ove ha luogo la interconnessione tra cellule e microambiente. Ciò implica ovviamente l'adozione di nuove premesse e nuovi modelli metodologici. La linea in questa direzione è stata già tracciata dalla Tissue Organization Field Theory (TOFT), per la quale il cancro nasce come conseguenza di un alterato rapporto tra le cellule e il loro ambiente, coinvolgendo stimoli sia biofisici quanto molecolari. Questa nuova impostazione può efficacemente risolvere i paradossi e le contraddizioni accumulatesi negli studi di cancerologia.

***Parole chiave**: Microambiente tumorale, TOFT, reversione neoplastica, mutazioni, biologia dei sistemi*

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The truth is corrupted when you
forget the process from which
truth concretely emerges
N.G. Dàvila

Introduction

Cancer is usually portrait – in many scientific papers, textbooks and even in popular culture – as a special kind of "genetic disease"(Reece et al., 2011). Namely, cancer is generally considered arising from "genetic changes", involving somatic mutations that lead to chromosomal aberrations and "new" phenotypic traits (Hanahan and Weinberg, 2000). Eventually, those features enable cells in recovering full motility, invasiveness and metastatic capability. Yet, it is quite disturbing that such a theory – the Somatic Mutation Theory of Carcinogenesis (SMT) – is deemed to be "a fact": an undisputed and, even worse, an unquestionable fact that has represented, in the last 40 years, the mainstream of cancer research.

The SMT envisions understanding cancer at the cellular level of organization, while claiming that cancer is a problem of regulatory control of cell proliferation and invasiveness, mainly due to mutations and/or deregulation of special classes of genes, i.e., oncogenes and suppressor genes. While SMT has fostered a gigantic and meaningful development of molecular-based technologies, the data accumulated through such approach generated evidence that openly contradicted its adopted premises (Backer, 2014).

Yet, by allowing a theory to be considered as an "established fact", any contradictory result is discarded as "irrelevant", alternative explanations are viewed as unwarranted, or, even worse, as "heretic." Indeed, /contemporaneous cancer research is witnessing a rise in the "dogmatic attitude" that regards concurrent explanatory theories no differently from how the Copernican theory was considered by the Ptolemy's followers. That is a blameworthy stance, not only from an epistemological point of view, but also in practical terms. It is a fact – and not a mere opinion – that current treatments, grounded on the aforementioned SMT paradigm are disappointing, asonly a slight advantage in overall survival rate since the introduction of the so-called target(gene)-based drugs (1991-2007, Fig. 1) has been documented (American Cancer Society, 2010). Indeed, despite some progress (some of which have been attained by rediscovering natural products, like retinol derivatives (Warrell et al., 1991), conventional as well as "innovative" chemotherapeutic protocols failed in obtaining significant improvement in overall survival, given that the death rates from the prevailing tumors (breast, colon, and prostate cancers) have remained stable (Autier et al., 2011). In a broader sense, there is a perception that cancer research is not progressing as fast as might be hoped from the financial investment in research (Hawkes, 2011). That evidence prompted commentators to suggest that we are losing the "war on cancer" (El-Deiry, 2013).

Because current approaches to explain and treat cancer are not working as well as might be expected, alternative approaches should be considered. Although this might sound reasonable, there are a large number of organizations heavily invested in maintaining the status quo. Therefore, both organizations (Big Pharma and hospitals) and individual researchers may be more interested in fostering irrelevant but easily publishable work on the minutiae of a gene transcription pathway in a genetically manipulated mouse, instead of exploring unchartered alternatives (Seymour and Mothersill, 2013). To afford such an endeavor, a revolution in both the currently prevailing experimental and clinical cancer paradigms is needed.

Based on this candid interpretation of facts, it stands to reason to propose that clinical and pharmacological studies should be redesigned, going back to human data from patient or epidemiologic investigation. Nonhuman data should be treated with caution and evaluated critically in the context of what the human data really show. This is especially true as data obtained *in vitro* or from animal studies, are usually derived from inbred tumor-prone, tumor cell-injected, or knockout rodent models, all of them of limited relevance tohuman populations within which cancers actually develop. Additionally, it must be stressed that animal experiments are largely designed to confirm and strengthen the current model, not to formulate or infer new hypotheses (Le Fanu, 1999). As a result of these misguided experimental and clinical approaches, research aims become increasingly focused on describing trivial molecular details, while scientists who adopt different, alternative, integrated-systemic approaches in cancer studies aimed at considering the organism as a whole often can't get funding.

Yet, it is note of worth that even long-time committed SMT supporters have recently acknowledged that the gene-based paradigm is facing increasing shortfalls and contradictions that make it no longer productive. Accordingly to R.A. Weinberg, the accumulated evidence did not turn out to vindicate explanations proposed by SMT. Quoting him, "half a century of cancer research had generated an enormous body of observations […] but there were essentially *no insights into how the disease begins and progresses*" (Weinberg, 2014). Despite the expectations raised by "the Ames' axiom ('substances act as carcinogens because they have mutagenic activity'), it shortly turned out that most powerful carcinogens are actually not mutagen"; "but fortunately – as Weinberg candidly admits – *I and others were not derailed by discrepant facts*". Indeed, a whole series of "discrepant facts" were ignored, while acknowledging that their realistic evaluation would have flawed the dominant paradigm. Yet, despite this realization, the search for mu-

tated oncogenes and/or tumor suppressor genes continued unabated up to the present. "But even this was an *illusion*, as only became apparent years later […] the identities of mutant cancer-causing genes varied dramatically from one type of tumor to the next […] Each tumor seemed to represent a unique experiment of nature". Indeed, experimental data provided so far urge us to revisit the role of gene mutations in cancer, suggesting that mechanisms for cancer initiation are broader differs from than is typically thought (Versteeg, 2014; Satgé, 2013).

Paradoxes

A renewed appreciation for paradoxes – i.e. statements that apparently contradict itself and 'yet might be true' – may shed light into this controversy. As pointed out by S. Baker (Baker and Kramer, 2007), current studies on cancer are precisely missing the paradoxical aspects of carcinogenesis for which there is no likely explanation under the Somatic Mutation Theory. Yet, these "paradoxes", offer opportunities for new research directions and leave room for alternative explanations, such as provided by the Tissue Organization Field Theory (TOFT) (Soto and Sonnenschein, 2011), which posits that cancer arises from the deregulated interplay among cells and their microenvironment. According to TOFT, the microenvironment represents the physical-biochemical support of the morphogenetic field which drives epithelial cells towards differentiation and phenotype transformation, according to rules understandable only by means of a systems approach (Soto and Sonnenschein, 2012). Not only the microenvironment-cells interplay is a matter of "signaling interaction", but also it involves biophysical factors and field-based effects, usually overlooked by the current scientific mainstream (Bizzarri et al., 2013). Lesser attention has been given to the explicitly highlighted premise of TOFT that states that the default state of all cells is *proliferation*. Notwithstanding, by challenging the implicit premise included in SMT that assumes that the default state of cells in metazoans is *quiescence*, it makes TOFT standalone from other theories of carcinogenesis. Briefly, TOFT considers that cancer is a tissue-based disease and adopts proliferation as the default state of all cells. This latter aspect of TOFT has been discussed at length elsewhere (Soto and Sonnenschein, 2011).

SMT supporters advocate that *had hoc* hypotheses should explain the observed contradictions, or even have proposed to reformulate SMT by adding new "parameters" (or "hallmarks"), that in fact represent epicycles of yore, by analogy with the Ptolemy-Copernicus controversy (Sonnenschein and Soto, 2006). Yet, the existence of a paradox merely points to the fact that the phenomenon under observation cannot be explained by SMT, and requires hence a different framework to be properly interpreted. Next we will schematically reconsider a few, key-elements on which the edifice of SMT is build.

Mutations

Cancer cells display a wide and ever changing set of spontaneous and induced somatic mutations. These features have been interpreted in causative terms, i.e. the gain or loss of function due to mutation(s) in one or more genes is likely to enact specific cell functions/dysfunctions (Sorsa, 1980). However, identification of such mutations indicates association *and not causation*. Thus, the supposed link in between gene mutation and cancer onset is, at the best, only presumptive.

Indeed, artificial ectopic over expression of at least four genes does not suffice to convert human normal cells into tumor cells (Morales et al., 1999; Li R. et al., 2000), as it was previously reported (Hahn et al., 1999). Oncogene-mediated cancer transformation is obtained in animal cells with a relatively high frequency, whereas human cells show to be highly resistant to such experimental manipulations (Holliday, 1996).Mathematical approaches have outlined how, as the number of gene products required to produce a particular phenotype increases, the effect of varying any one of these products becomes quite small (Kacser and Burns, 1981).

Furthermore, "mutated" genes (like K-*ras*) have been found only in a fraction of cancer cells, and a compelling body of evidence unambiguously demonstrated that a proportion ranging from 10 up to 40% of cancer cells did not show mutations (Versteeg, 2014; Greenman et al., 2007; Kan et al., 2010; Imielinski et al., 2012). Moreover, mutations are not always verified during the clonal expansion of cancer cells (Konishi et al., 1995; Baisse et al., 2001; Park et al., 1995; Szollosi et al., 1995). This means that a tumor is not a clone in which cells carry and transmit to their progeny the accumulated set of mutations: indeed, tumors are polyclonal and their genomic fingerprint has been demonstrated to be highly unstable, and continuously changing when cells are cultured *in vitro*(Shah et al., 2012). Additionally, cancer cells retain tumorigenicity (Plattner et al., 1996) and metastatic capability (Albino et al., 1984), even after spontaneous loss of the K-*ras* gene. Even more unexpected, genetic alterations believed to be associated with malignant tumors have also been described in normal tissues (Whashington et al., 2000; Lupski, 2013; Zhang et al., 1997). These examples suggest that genetic alterations found in cancerous tissues are not cancer-specific, given that they are frequently observed in normal tissues, and mostly in tissues affected by reactive or inflammatory processes (Hernández et al., 2010; Yamanishi et al., 2002).These are a truly unexpected findings that openly contradicts SMT, but just as surprisingly, they have been only rarely appreciated in their proper meaning.

Another outstanding case in point is represented by mutations associated with tobacco smoking. The main, critical

target for chemical constituents of tobacco is represented by the K-*ras* oncogene (Schuller, 2002). Among lung cancers, lung adenocarcinoma presents the highest frequency of K-*ras* mutations (Catalogue Of Somatic Mutations In Cancer). However, quite unexpectedly, such cancer type shows a weaker association with tobacco smoking than other pulmonary cancers (Sasco et al., 2004); moreover, adenocarcinoma is the less common histology type of lung cancer, a tumor type whose risk is strongly increased by smoking, even when (a further paradox!) adenocarcinoma is the commonest histological type of lung cancer in non-smokers (Khuder et al., 2001). Therefore, the paradoxical conclusion is that tobacco smoking induces lung cancer mainly through non-mutational mechanisms: "tobacco smoking increases the risk of having K-*ras* mutations only in lung adenocarcinoma; and that smoking influences the risk of pancreatic and colorectal cancer through events other than K-*ras* mutations"! (Porta et al., 2009).

Even data obtained by treating cancer patients with drugs allegedly designed to specifically target well-known mutated genes provided confused results. Namely, Imatinib, an inhibitor of the BCL-ABL oncogene located within the Philadelphia chromosome, has been demonstrated to successfully hamper leukemia cell growth. Yet, paradoxically cells *without* this mutation in the Philadelphia chromosome have a clonal advantage in culture over cells bearing the mutation (Coulombe et al., 1983). That result call into the question the role played by the oncogene in allowing unrestrained growth. Imatinib may alternatively exerts its antineoplastic effects trough different mechanisms, affecting alternative cancer cells properties (like metabolism) (Gottschalk et al., 2004), or by modulating the tumor microenvironment (Weisberg and Griffin, 2012). Both effects can be accommodated by TOFT, while can hardly be explained by SMT (Zhang et al., 2013).

One more evidence arguing the irrelevance of mutations during the carcinogenic process comes from studies performed on myeloid leukemia. The abnormal fusion tyrosine kinase BCR-ABL acts as an "oncogene" and it is deemed to be the key-initiating factor in myeloid onset. Inhibition of the corresponding oncoproteins by means of tyrosine kinase inhibitor (TKI) can indeed lead to significant responses, yet without achieving any benefit in terms of increased survival. This latter failure has been ascribed to the fact that a reservoir of cancer stem cells still proliferate because they lack the allegedly targeted-mutated gene and are therefore insensitive to the TKI (Pellicano et al., 2014; Jiang et al., 2007)! Thus, following this rationale, we are facing a very troublesome result, that is, myeloid cells become transformed by an oncogene that curiously, is absent among the cancer stem cell population, from which cancer is thought to originate!

Finally, although genetic changes in a relatively large number of target genes have been detected in tumors, in "the vast majority of cases it has not been possible to determine whether a particular mutation initiated the process, or occurred subsequent to the development of uncontrolled growth"(Balmain et al., 2000). Ideally, rigorous criteria should be applied before a causal link between carcinogenic exposure, genetic alteration and initiation of experimental carcinogenesis can be established: for instance, a) the target tissue should be exposed to the initiating carcinogen only once; b) the alleged mutation should be characteristic for each carcinogen used; and finally, c) other changes – in addition to the observed mutation – should be investigated in order to assign the causative role solely and exclusively to the single mutated gene, or to a stated combination of somatic mutations. Unfortunately, these criteria have been rarely considered in most available studies (Lawrence et al., 2013).This overwhelming lack of evidence led R. Versteeg to ask: "if not gene mutations, what else could cause cancer?" (Versteeg, 2014). It is arguably that mutations and/or changes in gene expression patterns arise as a secondary consequence of genetic instability, cytoskeleton distortion or disruption of the morphogenetic field (Bizzarri et al., 2008; Lorimore et al., 2003), as claimed by TOFT (Soto and Sonnenschein, 2014). Also, the SMT cannot explain why and how after exposure to well acknowledged genotoxic carcinogens, an exceedingly long latent period between carcinogen exposure and cancer initiation is required (Erson and Petty, 2006): that fact is overtly in contrast with what SMT claims, which predicts a rapid cancerous transformation when the carcinogen cause mutation(s).

In sum it can be concluded that mutations may be "associated", and thus should be deemed as "irrelevant to issues of tumor development" (Boland and Ricciardiello, 1999), or may have limited biological significance, and consequently "are not likely to play a dominant part in cancer" (Hua et al., 1997).

Non genotoxic carcinogenic agents

A meaningful paradox in carcinogenesis is represented by the increasingly recognized existence of powerful carcinogens acting through non-genotoxic mechanisms, i.e. without inducing any detectable point mutation (Lijinsky, 1990; Hernández et al., 2009). As it was candidly admitted by SMT supporters, despite the expectations raised by "the Ame's axiom ("substances act as carcinogens because they have mutagenic activity"), it was soon demonstrated that most powerful carcinogens are actually not mutagen" (Weinberg, 2014). It is noteworthy that this evidence emerged already since the 1940's, when I. Berenblum claimed that "the apparent correlation between mutagenic and carcinogenic activities, as noted in the case of physical agencies, has not been confirmed when extended to chemical agents, and can no longer be used as strong support in favour of the somatic cell mutation theory of cancer" (Berenblum and Shubik, 1949).

Non-genotoxic carcinogens have been shown to act as tumor promoters (1,4-dichlorobenzene), endocrine-modifiers (17beta-estradiol), receptor-mediators (2,3,7,8-tetrachlorodibenzo-p-dioxin), immune-suppressants (cyclosporine) or inducers of tissue-specific toxicity and inflammatory responses (metals such as arsenic and beryllium) (Weinstein, 1991; Lee et al., 2013). Yet, it is rather surprisingly that such paradox has only rarely been appreciated in all its implications, given that the existence of substances which induce cancer without affecting DNA undermines irretrievably the SMT paradigm.

One such particular case is represented by foreign body-based carcinogenesis (Moizhess, 2008) (FBC), i.e. the development of tumors in the proximity of inserted materials, devoid of intrinsic chemical activity. Relevance of such findings is nowadays increasing in connection with the recent description of human tumors arising around artificial prostheses, such as vascular ones (Alexander et al., 2006; IARC Monographs). In this regard, the most intriguing data point to the fact that the physical form of the implant (rather than its chemical nature) is the most significant parameter for tumor induction. In particular, it was found that highly tumorigenic polymeric plates exhibited lower carcinogenicity after perforation, while disintegration into small fragments resulted in almost complete loss of carcinogenicity (Tomatis, 1963; Karp et al., 1973). That enigmatic aspect of experimental carcinogenesis has been recognized at the beginning of the last century and for a while it has represented a prominent field of investigation (Brand et al., 1975). Many hypotheses were proposed to explain the mechanism of FBC carcinogenesis, but as none of them could realistically fit the theoretical boundaries provided by the SMT, interest on FBC has rapidly declined. Factually, there is no plausible SMT explanation for these results, while TOFT offers a sound explanation, given that insertion of a foreign body may likely disrupt normal cell-microenvironment interactions, leading to a localized tissue disorganization (Sonnenschein and Soto, 2000).

Spontaneous regression of Cancer

An impressive body of both clinical and experimental data have demonstrated that several cancers can undergo a spontaneous regression, reverting toward a normal phenotype. Spontaneous disappearance or differentiation of animal and human cancers, like stage-IV neuroblastoma, liver neoplasia (Tatematsu et al., 1983),breast tumors (Horii et al., 2005), and many others, have been hitherto reported (Papac, 1998; Challis e Stam, 1990). Similarly, several reports have shown that by placing cancerous cells into a "normal" microenvironment – i.e., by restoring a normal, strong morphogenetic field – the tumor phenotype may be reverted into a normal one, eventually enabling a de novo cell and tissue differentiating process. Cancer cells exposed to embryonic morphogenetic fields (Bizzarri et al., 2011; D'Anselmi et al., 2011; Pierce e Wallace, 1971) or cultured in 3D-reconstructed biological microenvironment mimicking the normal tissue architecture (Willhauck et al., 1980; Maffini et al., 2004; Krause et al., 2010), undergo entrenched processes of apoptosis and differentiation, eventually ending up into the reprogramming of a "normal" phenotype (Hendrix et al., 2007; D'Anselmi et al., 2013; Bissell et al., 2005; Kenny and Bissell, 2003). Usually, this evidence is either dismissed by SMT supporters, arguing that microenvironment may activate other unknown genetic pathways through unspecified ways, or else ignored, by considering it a "funny" exception. In fact, within the theoretical boundaries provided by SMT such results cannot be explained, and actually SMT advocates do not even pretend to do so. Indeed, if cancer onset were truly an event due to the accumulation of mutations in a few key-genes, once the threshold has been crossed there would be no way back towards normality. On the contrary, such paradoxical data constitute a pivotal element of TOFT, which posits that the microenvironment represents the physical-biochemical support of the morphogenetic field which drives epithelial cells towards differentiation and phenotype transformation (Bizzarri and Cucina, 2014).

Paradoxical behavior of "signaling" molecules

Molecular biology has been build upon the paradigm which posits that some biochemical compounds carry specific "information", acting so far as "biochemical signals" (Crick, 1958; Bailly and Longo, 2011). That approach implies to read biological phenomena according to rules and concepts formulated by the information theory, according to which the "biological signal" must be unambiguous – possessing therefore only one meaning – and be efficiently transduced – implying that the "signal" could overcome the surrounding noise, eventually counteracting other non-genetic cues and biophysical constraints. However, such interpretation has been called into question, given that it has encompassed many intractable contradictions (Longo, 2009; Longo et al., 2012). Namely, evidence is mounting that the so-called "signaling molecules" (growth-factors, receptors, oncogene products and so forth) do not exert a specific effect as it was previously thought, and eventually may trigger opposite, "paradoxical", activities. For instance, AKT, a kinase activated by PI3K, is considered a key mediator of several cell-survival and proliferation pathways, by influencing a number of downstream effectors. As such AKT is viewed as a prominent feature of cancer, while playing a pivotal role within SMT (Lo Piccolo et al., 2007). As a consequence, the inhibition of AKT activity is nowadays considered a promising therapeutic target. However, it is sobering to note that recent studies have identified an unexpected function of AKT in cancer cells. By using a different methodological approach, two distinct research groups have demonstrated that Akt acti-

vation may paradoxically lead to inhibition of cell motility and proliferation (Yoeli-Lerner et al., 2005; Irie et al., 2005). Similarly, p53 gene, considered the "guardian of the genome" (Lane, 1992), allegedly preserve cells from tumoral transformation, irreversible growth and immortalization when activated. However, curiously, in rats over-expressing the well-known K-*ras* oncogene, which is considered crucial in developing skin papillomas, p53 deletion almost completely abolish the carcinogenic effects supposedly exerted by K-*ras* (Greenhalgh et al., 1996)! Similar results have been reported by over-expressing p53 in mice exposed to chemical carcinogenesis (Wang et al., 1998). Interestingly, such a result is not ascribed to any specific "signal" triggered by the activated gene, but instead to a generalized genetic instability enacted by the artificial genome manipulation: this observation suggests that a system perturbation (i.e., the deregulation of the genome architecture) is more likely to be at the root of the transformation process in the presence of an appropriate stimulus (i.e., the chemical carcinogen).

By analogy, the NF-kB pathway activation, widely assumed o be a pivotal step in cancer progression, has demonstrated to exert outstanding anti-tumoral, paradoxical effects. Indeed, hepatocyte-specific ablation of Ikkb, a kinase required for the activation of NF-kB, resulted in a dramatic increase in hepatocellular carcinoma development, induced by the chemical carcinogen diethyl-nitrosamine, this now points to an antitumor effect of NF-kB in the liver. The authors of this report do not offer compelling explanations for these results while vaguely referring to the overstated fact that such "contradiction [e.g., the opposing roles of signaling molecules] underscores the complexity of hepatocarcinogenesis and predicts uncertainty in targeting these molecules" (Feng, 2012). Instead, such data highlight the unsustainability of the paradigm relying on the so-called "signaling molecules" and begs for an in depth reassessing of current theoretical modeling in an experimental approach that implicitly relies on the premises of SMT.

Even in humans bearing genetic diseases (like trisomy 21), gain or loss of genetic function due to mutation or gene deletion, are indeed subject to a strong modulating effect exerted by tissue constraints, as the cell microenvironment can efficiently enable or inhibit specific gene activities (Satgé and Bénard, 2008). We would propose, instead, that a relevant role for genes emerges only when the systems is experiencing a phase transition, like that occurring during differentiation and/or when cells acquire a new phenotype. These instances may explain why mutated genes are ineffective in resting tissues, and why the relevance of differentiating gene-related pathways (like the p53 system) can only be appreciated during certain developmental phases: these pathways may react differently according to their tissue-context (Lane and Benchimol, 1990; de Keizer et al., 2010; Bizzarri et al., 2013).

Further evidence about a paradoxical role played by molecular actors has been provided by studies on hyaluronan (HA) (Stern, 2005). Meanwhile the correlation among deposition of HA (in either tumor stroma or within cancer cells) is a widely accepted indicator of poor prognosis (Anttila et al., 2000), tissue concentration of hyaluronidase (the enzyme that degrade HA) paradoxically correlates directly with tumor aggressiveness (Posey et al., 2003).

Equally puzzling is the behavior of leucine-rich repeats and immunoglobulin-like domains protein 1 (LRIG1), an endogenous inhibitor of growth factor signaling and a proposed tumor suppressor (Powell et al., 2012). In epidemiologic studies carried out in Swedish patients, high LRIG1 expression was significantly associated with short overall and prostate cancer-specific survival, inconformity with the role attributed to this protein. In contrast, in US patients, high LRIG1 expression was significantly and unexpectedly associated with long overall survival (Thomasson et al., 2011). Authors of that observational study correctly concluded that the meaning as well as the activity of LRIG1 is tightly context-dependent and can be appreciated only by adopting a systemic approach, instead of a reductionist one. That is to say that a reductionist-based framework suffers from the vice of circularity and no cogent answer may be obtained when cause-and-effect based model are summoned in explaining complex systems (Isalan and Morrison, 2009).

Similar paradoxical behaviors have been recorded for others so-called oncogenes or anti-apoptotic factors. The well-known pro-survival protein Bcl-2 exerts an anticarcinogenic effect when activated in transgenic mouse over-expressing c-Myc (de La Coste et al., 1999). In turn, c-Myc, a widely recognized "oncogene", induces differentiation and apoptosis in embryonic human cells in a transcriptional activity-dependent manner (Sumi et al., 2007). The differentiating and pro-apoptotic activity of c-Myc is nowadays well established (Amati et al., 1994). However, this feature is difficult to reconcile with its pro-oncogenic effects (You et al., 2002). Again, to solve the puzzle one has to look closely to the tissue context, given that c-Myc levels and functions are likely to be modulated by cell density (Lee et al., 1995). Similar considerations can be developed about the paradoxical role played by Lysyl oxidase enzyme, regulated by the LOX gene. Evidence points out that LOX acts simultaneously as both a tumor suppressor and a metastasis promoter gene in cancer (You et al., 2002). That puzzling result can only be ascribed to differences in context (tumor-stroma, cell-stroma interactions, ECM stiffness), which finely tune the non-linear dynamics of LOX activity. Consequently, such complexity "precludes traditional microarray-based research to investigate tumor suppressor/metastatic promoting functions of LOX in human cancers" (Payne et al., 2007).

Perhaps the best studied example of molecular paradoxes in cancer is represented by TGF-β behavior (Moses

et al., 1990). Both anticancer as well as cancer-promoting effects have been alternatively ascribed to TGF-β, until it becomes clear that the "dichotomous" nature of this molecule can be understood only by looking at the tissue-context in which TGF-β is called upon to exert a biological function (Tian and Schiemann, 2009). Indeed, tumor stroma not only plays an important role during cancer initiation and progression, but also in determining whether TGF-β suppresses or promotes tumor formation (Bierie and Moses, 2006). That challenging puzzle can be solved by referring data to a higher (tissue) level of biological organization and by adopting a systems approach. For instance, TGF-β may trigger opposite outputs depending on the tissue stiffness: under mechanically unloaded conditions (floating matrices), TGF-β stimulated contraction directly as an agonist, and indirectly by pre-activating cells to express the myofibroblast phenotype, whereas, under mechanically loaded conditions (stressed matrices), TGF-β had no direct agonist effect on contraction (Grinnell and Ho, 2002). This example highlights how when the cell-microenvironment interactions are kept in consideration, apparently conflicting results end up as such, and paradoxes may likely find a compelling explanation.

Conclusion

Paradoxical results are not uncommon in cancer studies when interpreted from the SMT perspective. Yet, the accumulated weight of such paradoxes is carrying cancer researchers into a blind alley. As it was acknowledged by R.A. Weinberg, "we lack the *conceptual paradigms and computational strategies for dealing with this complexity*. And equally painful, we don't know how to integrate individual data sets, such as those deriving from cancer genome analyses, with other, equally important data sets, such as proteomics" (Weinberg, 2014). Weinberg's acknowledging of the failure of reductionist hypotheses to resolve cancer complexity is yet another confirmation of the time honored wisdom that the knowledge of the parts does not imply knowledge of the whole. During the last four decades, biologists at large have adopted a reductionist-based framework (Cornish-Bowden, 2011) according to which "information" flows unidirectionally (from DNA to proteins, from genotype to phenotype), and thereby form and functions of organisms depend solely on "genetic information", meaning 'digital' information. Nevertheless, biological interactions take place at different, entrenched levels, where lower level (molecular) processes are shaped by non-linear dynamics, and are strongly influenced by higher-level organization constraints (Dinicola et al., 2011; Soto et al., 2008).

Therefore, a profound reassessment of carcinogenesis model – as such proposed by TOFT – and the adoption of a systems biology approach, are both urgently needed (Bizzarri, 2014). A good starting point would address those paradoxes which defy the classical model upon which carcinogenesis studies are grounded. Ignoring these paradoxes is no longer sustainable. Avoiding facing obvious conundrums is tantamount to saying that the prevailing theory holds in all instances except the paradoxical ones, where SMT is openly contradicted. By "removing" paradoxical results we deprive ourselves of the opportunity to achieve real progress. Making rigorous science entails asking the right questions, and identifying the right level of biological organization for proper answers. Instead, it seems as if we are lost, concentrated in describing details within a molecular maze. A system approach able to grasp the overall complexity of cancer – TOFT – has been proposed at least 15 years ago (Sonnenschein and Soto, 1999). Such model deserves to be explored and tested in depth. This implies an open-minded attitude from Academia, and, for sure, appropriate financial opportunities, without which no chance of resolving the cancer puzzle are realistic. But, first of all, we have to regain the freedom of thought, rediscovering the risks and the thrills of exploring uncharted territories.

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