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Systems Biology for Understanding Cancer Biology

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During last decades the theoretical framework in carcinogenesis studies has been provided by the Somatic Mutation Theory (SMT) [1]. SMT envisions understanding cancer at the cellular level of organization, by claiming that cancer is a problem of regulatory control of cell proliferation and invasiveness, mainly due to mutations and/or deregulation of a specific class of genes. Even though SMT has fostered a meaningful development of molecular-based technologies, on the other hand that approach has encompassed an increasing number of experimental results that contradict its premises [2]. Additionally, current therapeutic approaches based on SMT have been proven to be ineffective in clinical cancer management to the extent that, for now, is urgently required a careful rethinking of our treatment strategies [3,4]

Among others, R.A. Weinberg has substantially contributed in popularizing the SMT among scientists. However, Weinberg himself has recently called into question the entire theoretical construct of SMT. Quoting him, he stated that "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*"[5]. 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 [6]. Yet, despite this realization, the search for mutated 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". Unfortunately "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". Indeed, during the last four decades, Biology has implicitly accepted to be grounded on a reductionistic-based framework [7] according to which "information" flows unidirectionally from genotype to phenotype, and thereby form and functions of organism depend solely on "genetic information", deemed as 'digital' information. However, biological interactions take place at different, entrenched levels, where lower molecular processes are shaped by non-linear dynamics, and are strongly influenced by higher-level organization constraints [8] Thereby, as we are actually unable to grasp such overwhelming complexity, we are also unable to set a reliable theory of biological organization [9].

This is especially true in carcinogenesis studies, where both experimental modelling and theoretical framework have been for long time undisputedly dominated by SMT [10] notwithstanding few alternative explanation have been proposed, grounded on very different biological premises and epistemological settings [11-13]

Those findings have important methodological implications. First, cell function and behaviour cannot be longer studied in isolation, without considering their three-dimensional microenvironment [14], which could enable in integrating data coming from different levels of observation [15]. Second, biophysical cues acting on tissue and cyto/nucleo-skeleton architecture, must be adequately weighted and thoroughly investigated [16]. Third, instead of "single" and "simple" molecular and genetic changes, we have to investigate complex non-linear behaviour of gene/proteomic networks, involving both epithelial and stromal components. This approach represents the updated interpretation of the old concept of homeostasis, currently re-interpreted as auto-conservation, functional stability, evolvability or robustness within a Systems Biology perspective [17]. Indeed, given that homeostasis is dramatically threatened or even disrupted in the course of several diseases, to understand such processes we obligatory require a Systems Biology approach to study non-linear spatio-temporal systems with multiple levels of structural and functional organization.

A widely accepted paradigm will hardly be dropped before a considerable amount of paradoxes and contradictions has been gained, as Kuhn taught us [18]. This moment, as patently admitted even by SMT followers, seems to have come. Thereby, a true progress may be now disclosed embracing new theoretical perspectives as well as methodological frameworks, like those provided by Systems Biology [19,20].

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