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Review

Cancer stem cells display extremely large evolvability: alternating plastic and rigid networks as a potential Mechanism Network models, novel therapeutic target strategies, and the contributions of hypoxia, inflammation and cellular senescence

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ABSTRACT

Cancer is increasingly perceived as a systems-level, network phenomenon. The major trend of malignant transformation can be described as a two-phase process, where an initial increase of network plasticity is followed by a decrease of plasticity at late stages of tumor development. The fluctuating intensity of stress factors, like hypoxia, inflammation and the either cooperative or hostile interactions of tumor inter-cellular networks, all increase the adaptation potential of cancer cells. This may lead to the bypass of cellular senescence, and to the development of cancer stem cells. We propose that the central tenet of cancer stem cell definition lies exactly in the indefinability of cancer stem cells. Actual properties of cancer stem cells depend on the individual "stress-history" of the given tumor. Cancer stem cells are characterized by an extremely large evolvability (i.e. a capacity to generate heritable phenotypic variation), which corresponds well with the defining hallmarks of cancer stem cells: the possession of the capacity to self-renew and to repeatedly re-build the heterogeneous lineages of cancer cells that comprise a tumor in new environments. Cancer stem cells represent a cell population, which is adapted to adapt. We argue that the high evolvability of cancer stem cells is helped by their repeated transitions between plastic (proliferative, symmetrically dividing) and rigid (quiescent, asymmetrically dividing, often more invasive) phenotypes having plastic and rigid networks. Thus, cancer stem cells reverse and replay cancer development multiple times. We describe network models potentially explaining cancer stem cell-like behavior. Finally, we propose novel strategies including combination therapies and multi-target drugs to overcome the Nietzschean dilemma of cancer stem cell targeting: "what does not kill me makes me stronger".

Abbreviations: AKT, RAC-alpha serine/threonine protein kinase; BMI1, polycomb ring finger oncogene; C/EBP, CCAAT/enhancer binding protein; CD34, hematopoietic progenitor cell antigen CD34; CD38, CD38 ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase; CD133, prominin-1 hematopoietic stem cell antigen; CD271, low affinity nerve growth factor receptor; MYC, avian myelocytomatosis viral oncogene homolog; MYD88, myeloid differentiation primary response protein; BRAF, B-Raf proto-oncogene serine/threonine-protein kinase; E2F, E2F transcription factor; HRAS, Harvey rat sarcoma viral oncogene homolog, small GTP-binding protein; IL-6, interleukin 6; IL-8, interleukin 8; KLF4, endothelial Kruppel-like zinc finger protein; KRAS, Kirsten rat sarcoma 2 viral oncogene homolog, small GTP-binding protein; Lgr5, leucine-rich repeat-containing G-protein coupled receptor 5; MAP2K3, MAPK/ERK kinase 3; miR, microRNA; NANOG, early embryo specific expression NK-type homeobox protein; NFκB, nuclear factor kappa-B; OCT4, octamer-binding transcription factor 4; CDKN2A, CDK4 inhibitor p16-INK4; p53, p53 tumor suppressor; PI3K, phosphatidylinositol 4,5-bisphosphate 3-kinase; PTEN, phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase; RAS, rat sarcoma viral oncogene homolog, small GTP-binding protein; SOX2, transcription factor; TGF-ß, transforming growth factor beta; WNT, Wingless and int like protein; ZEB, zinc finger E-box binding homeobox proteins.

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1. Cancer as a network development disease

Malignant transformation is increasingly described as a systems-level, network phenomenon. Both healthy and tumor cells can be perceived as networks. Nodes may be the amino acids of cancer-related proteins, where edges are related to secondary chemical bonds. Nodes may also be defined as protein/RNA molecules or DNA-segments, where edges are their physical or signaling contacts. In metabolic networks, nodes are metabolites and edges are the enzymes, which catalyze the reactions to convert them to each other [1–3]. Most of the statements of this review may characterize all these molecular networks of tumor cells and cancer stem cells.

As stated already by Virchow in 1859 [4], cancer is a developmental process. Cancer cells are products of a complex series of cell transformation events. The starting steps are often mutations or DNA-rearrangements, which destabilize the former cellular phenotypes. As a result, a cell population with a large variability in chromatin organization, gene expression patterns and interactome composition is formed [5–9]. In this process, changes in network structure and dynamics play a crucial role.

This review will focus on the large-scale network rearrangements during cancer development—and the emergent, systems-level changes they develop. We will show that changes in network plasticity (and its opposite: network rigidity) may explain central tenets in both cancer development and cancer stem cell behavior. Network plasticity (or in other words network flexibility) can be defined at the level of both network responses and structure [7,10] as it will be detailed in Section 2.

2. Malignant transformation proceeds *via* states characterized by increased and decreased network plasticity

2.1. Initial increase of network plasticity is followed by a decrease of network plasticity at late stages of carcinogenesis

In our earlier works [3,11,12], summarizing several pieces of evidence we proposed that malignant transformation is a two-phase process, where an initial increase of network plasticity is followed by its decrease at late stages of carcinogenesis. The phenotype of the already established, late-stage cancer cells is still more plastic and immature than that of normal cells, but may often be more rigid than the phenotype of the cells in the intermediate stages of carcinogenesis.

In this concept, network plasticity (or in other words functional network flexibility) can be determined either at level of network responses (network dynamics, attractor structure) and at the level of network structure. The network has a high plasticity at the level of its responses, if small perturbations induce large changes in network structure and dynamics [7,10]. At the level of network, structure network plasticity depends on the internal degrees of freedom of network nodes. Degrees of freedom are reduced by dense clusters, like cliques, or by intra-modular node position. Degrees of freedom are also related to specific network properties: e.g. in transportation-type networks (like metabolic networks) an additional edge may increase the degree of freedom, while in connection type networks (like interactomes) an additional edge may decrease the degree of freedom. The numerical characterization of network plasticity both at the network response and network structure levels is an exciting area of current studies (see more in [10]).

Sources and signs of the initial increase of network plasticity in cancer development are summarized in Table 1 [5,7,13–30]. These sources and signs are related to each other, and might not happen independently. Moreover, Table 1 shows a self-amplified growth of network disorder during tumor development. Self-amplification occurs, when the increased disorder of nodes causes a disorder of their networks, which amplifies the disorder of the nodes further. These synergistic processes cause an accelerated decrease of system-constraints, with a parallel increase in entropy and the degrees of freedom both at the level of the individual nodes and their networks. All these changes lead to the development of more plastic cellular networks in the early phase of cancer. The early stage of cancer development, characterized by an increase of network plasticity, may correspond to the "clonal expansion" phase and the appearance of tumor initiating cells. Such plasticity increase may characterize multiple clonal expansions occurring in some cancer types.

Late stage carcinogenesis is characterized by a decrease of network plasticity reflected by decreasing entropy both at the interactome and signaling network level (such as in case of comparing colon carcinomas to adenomas; Hódsági et al. and Módos et al., unpublished observations). Late stage tumor cells may represent either late stage primary tumor cells, or metastatic cells, which already settled in their novel tissue environment. These findings are in agreement with the recent data of Aihara and co-workers [31,32] showing a transient decrease of entropy of human bio-molecular interaction network during B cell lymphoma, hepatocellular carcinoma and chronic hepatitis B liver cancer development. It is yet to be shown, whether the other types of plasticity increases listed in Table 1 for early stage cancer cells are also reversed in late stage cancer cells.

The dual changes described above correspond well to various steps in the transition to the cancer-specific states, termed as "cancer attractors" by Stuart Kauffman in 1971 [33]. Cancer cells have to first cross a barrier in the quasi-potential (epigenetic) landscape. This barrier might be lowered by mutations or epigenetic changes [5], but its bypass requires a transient destabilization of the transforming cell. This destabilization leads to a more plastic phenotype. This is followed by the stabilization of the cancer cell in the cancer attractor invoking a more rigid phenotype. Importantly, the attractor structure itself may undergo gross changes during cancer development, due to changes in network structure, dynamics and interactions with the environment.

The increase and decrease of network entropy resembles to that observed in cell differentiation processes, where an initial increase of entropy of co-regulated gene expression pattern was followed by a later decrease [34]. An analogous set of events happens in cellular reprogramming, where an early, very heterogeneous, stochastic phase is followed by a late phase, which is programmed by a hierarchical set of transcription factors [35]. Plastic/rigid phenotypes of early/late phases may correspond to the proliferative/remodeling phenotypes of cancer cells obtained by gene expression signature analysis [36]. Importantly, the proliferative/remodeling phenotype duality is very similar to the duality of proliferative/quiescent states of cancer stem cells, which we will discuss in Section 3.

2.2. Increase and decrease of network plasticity may alternate in cancer development

The initial increase and later decrease of network plasticity is not displayed uniformly by the heterogeneous cell populations of tumors. Tumors may harbor early phase (plastic) and late phase (rigid) cells at the same time. Importantly, cancer cells in late phase may switch back to an early phase of development [7,26,28]. Thus, tumor cell populations may often be characterized by reversible switches between plastic and rigid network states. Cancer stem cell networks may alternate between plastic and rigid states very intensively, as we will describe in Section 3.

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