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Review

Cancer-related networks: A help to understand, predict and change malignant transformation

Q1 Peter Csermely[a,*], Tamás Korcsmáros[b]

[a] Department of Medical Chemistry, Semmelweis University, P.O. Box 260, H-1444 Budapest 8, Hungary
[b] Department of Genetics, Eötvös Loránd University, Pázmány P. s. 1C, H-1117 Budapest, Hungary

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ABSTRACT

Cancer is increasingly described as a systems-level, network phenomenon. Genetic methods, such as next generation sequencing and RNA interference uncovered the complexity tumor-specific mutation-induced effects and the identification of multiple target sets. Network analysis of cancer-specific metabolic and signaling pathways highlighted the structural features of cancer-related proteins and their complexes to develop next-generation protein kinase inhibitors, as well as the modulation of inflammatory and autophagic pathways in anti-cancer therapies. Importantly, malignant transformation can be described as a two-phase process, where an initial increase of system plasticity is followed by a decrease of plasticity at late stages of tumor development. Late-stage tumors should be attacked by an indirect network influence strategy. On the contrary, the attack of early-stage tumors may target central network nodes. Cancer stem cells need special diagnosis and targeting, since they potentially have an extremely high ability to change the rigidity/plasticity of their networks. The early warning signals of the activation of fast growing tumor cell clones are important in personalized diagnosis and therapy. Multi-target attacks are needed to perturb cancer-specific networks to exit from cancer attractors and re-enter a normal attractor. However, the dynamic non-genetic heterogeneity of cancer cell population induces the replenishment of the cancer attractor with surviving, non-responsive cells from neighboring abnormal attractors. The development of drug resistance is further complicated by interactions of tumor clones and their microenvironment. Network analysis of intercellular cooperation using game theory approaches may open new areas of understanding tumor complexity. In conclusion, the above applications of the network approach open up new, and highly promising avenues in anti-cancer drug design.

1. Cancer and the malignant transformation process as a network phenomenon

Malignant transformation is increasingly described as a systems-level, network phenomenon. Healthy and tumor cells can be understood as networks, if their nodes and edges are precisely defined. Nodes may be amino acids of cancer-related proteins, where edges are their distances in the 3D protein structure. Nodes may 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. Analysis of network topology and, especially, network dynamics can predict novel anti-cancer drug targets. Incorporation of personalized data, such as mutations, signalome (e.g. phosphoproteome) or metabolome profiles to molecular networks may enhance patient- and disease stage-specific drug targeting in anti-cancer therapies [1–3]. Patient specificity can differentiate network behavior in at least four different levels: (A) at the level of the genetic background (e.g., single-nucleotide polymorphisms and other mutations); (B) at the level of gene expression changes (caused by e.g. transcriptional, epigenetic or microRNA mediated changes); (C) at the level of the microenvironment (e.g. neighboring cells, tissue structure, etc.); and finally (D) by exogenous signals (e.g. nutrients or drugs), which all provide increments to the patient-specific, context-dependent responses to anti-cancer therapy [4–6]. Contributions to this special issue address all the above scenarios.

Cancer is a complex disease, where magic-bullet type drugs may often fail. Degenerate (partially redundant) signaling pathways are hallmarks of cancer robustness. Thus an inhibitor of a particular hallmark of cancer may not be sufficient to block a related function. Moreover, inhibitors of a specific cancer hallmark may strengthen another hallmark, like certain types of angiogenesis inhibitors increased the rate of metastasis. In most failures of anti-cancer

Abbreviations: miRNA, micro RNA; PRISM, PRotein Interactions by Structural Matching; RNAi, RNA interference.

* Corresponding author.
E-mail address: csermelynet@gmail.com (P. Csermely).

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therapies, either system robustness or off-target effects prevented the accomplishment of the desired pharmacological goal. Combination therapies and multi-target drugs may both overcome system robustness and provide less side-effects [7–12]. Moreover, tumors contain a highly heterogeneous cell population that could be efficiently inhibited only by drug combinations. Cell populations and their drug responses can be perceived as a bipartite graph, where cell populations and drugs form two different node sets having no connections inside them, but being connected, when a drug inhibits a cell population. Applying minimal hitting set analysis allowed the search for effective drug combinations at the inter-cellular network level [13]. Last but not least the billion development routes to cancer states define a highly heterogeneous patient profile depending on personal genetic background and life-history. As a recently published example, consensus-based unsupervised clustering of gene expression profiles from 1290 colorectal cancer tumors identified 6 clinically relevant disease subtypes, where different treatment modalities were proved to be optimal [14]. The network analysis approaches described in this special issue may enrich and extend these studies.

2. Network descriptions of cancer from protein structures to cellular communities

In the opening contribution of this series, Lauffenburger and co-workers [15–17] analyze the richness of cancer RNA interference (RNAi) studies from the network point of view. As they summarize: "Interpreting RNAi results in a network framework instead of merely as individual 'hits' or 'targets' leverages contributions from all hit/target contributions to pathways via their relationships with other network nodes". This leads to the integration of multiple data sets of experimental results, improved target identification, as well as the creation of testable hypotheses for therapeutic development.

Another highly powerful genomic analysis tool, next generation sequencing is addressed by Bates and co-workers [18,19]. "Network analysis approaches have become an invaluable tool to predict and interpret mutations that are associated with tumor survival and progression. Our understanding of cancer mechanisms is further enhanced by mapping protein structure information to such networks." A typical solid tumor harbors tens to hundreds of non-synonymous somatic mutations, where subgroups of tumor cells differ in their mutation spectrum: approximately 50% of the mutations found in one biopsy may not be shared with other biopsies from the same patient. Network analysis may provide sub-groups of this large diversity. The development of analytical tools that are able to quantify the dynamic impact of mutations on a network will bring valuable insights into the disease mechanism of mutations at the molecular level.

The metabolism of cancer cells is adapted to meet their proliferative needs in predominantly anaerobic conditions. Sharma and König [20,21] give a summary of the methodology of metabolic modeling proven to be useful for modeling the deregulated metabolism of cancer cells. They also evaluate statistical analyses identifying cancer-specific metabolic pathways.

Signaling-related anti-cancer therapies increasingly outnumber metabolism-related chemotherapy options. From the network point of view this trend is due to the high complexity of signaling networks in humans, and to the increased selectivity of signaling interactions as compared to metabolism-related targeting [3]. From the three signaling-related papers of the issue Tsai and Nussinov [3,22,23] describe the molecular basis of protein kinase targeting in anti-cancer therapies. They "exploit a conceptual framework explaining why suppressed kinase activity will selectively kill only the so-called oncogene 'addicted' cancer cell, while sparing the healthy cell." Tsai and Nussinov argue that "understanding the detailed activation mechanism of individual kinases is essential to relate the observed oncogenic alterations to the elevated constitutively active state, to identify the mechanism of consequent drug resistance, and to guide the development of the next-generation inhibitors." They also discuss "scenarios of drug resistance and relapse by compensating lesions that bypass the inactivated pathway in a vertical or horizontal fashion", and conclude that personalized combination therapies are needed to overcome the robustness of kinase-related signaling pathways.

Chronic inflammation is increasingly understood to play a major role in all phases of tumorigenesis, including tumor initiation, promotion and metastasis. Nussinov and co-workers [3,22,24,25] describe the Toll-like receptor pathway playing a central role in inflammation and carcinogenesis. They use the PRotein Interactions by Structural Matching (PRISM, [24]) tool to reveal a structure-based orchestration of the Toll-like receptor pathway highlighting the role of myeloid differentiation primary response protein, MyD88.

Autophagy, a highly regulated self-degradation process of eukaryotic cells, is a context-dependent tumor-suppressing mechanism that can also promote tumor cell survival upon stress and treatment resistance. Kubisch et al. [3,26–28] show "how systems-level knowledge on autophagy regulation can help to develop new strategies and efficiently select novel anti-cancer drug targets." Focusing on the protein interactors and transcriptional/post-transcriptional regulators of autophagy they list several network resources, benchmark the presence of autophagy core proteins in them, and "point out that a context-dependent modulation of autophagy would be favored in anti-cancer therapy, where autophagy is stimulated in normal cells, while inhibited only in stressed cancer cells." They introduce the concept of "regulo-network drugs targeting specific transcription factors or miRNA families identified with network analysis. The effect of regulo-network drugs propagates indirectly through transcriptional or post-transcriptional regulation of autophagy proteins, and, as a multi-directional intervention tool, they can both activate and inhibit specific proteins in the same time. The future identification and validation of such regulo-network drug targets may serve as novel intervention points, where autophagy can be effectively modulated in cancer therapy."

Gyurkó et al. [3,29,30] propose that malignant transformation is a two-phase process, where an initial increase of system plasticity is followed by a decrease of plasticity at late stages of carcinogenesis as a model of cellular learning. They describe the hallmarks of increased system plasticity of early, tumor initiating cells, as increased noise, entropy, conformational and phenotypic plasticity, physical deformability, cell heterogeneity and network rearrangements. Importantly, a more ordered system is generally less controllable than a disordered one [31], which prompts Gyurkó et al. to warn that (A) therapeutic interventions of the early, more plastic stage of carcinogenesis are more efficient than those against late-stage tumors; (B) late-stage tumors should be attacked by an entirely different strategy than early-stage tumors. They suggest that plastic/flexible networks of early phase cancer development need a hit on their central nodes, while rigid networks of late stage primary tumors or established metastases should be attacked by the network influence strategy, such as by edgetic, multi-target, or allo-network drugs [3,29,32]. They argue that application of early stage-optimized anti-cancer drugs to late-stage patients may be a reason of many failures in anti-cancer therapies. Importantly, heterogeneous cancer cell populations may harbor early- and late-stage tumor cells at the same time. The hypotheses presented in the paper underlie the need for patient-specific multi-target therapies applying the correct ratio of central hits and network influences [3] — in an optimized sequence.

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