6 Adaptation of Molecular Interaction Networks in Cancer Cells

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Overview

Network theory as part of complex systems theory has over the past decades developed powerful tools to analyze and make sense of the enormous amounts of molecular interaction data obtained by modern molecular biology methods at the DNA, RNA, and protein levels. These complex network models of intracellular molecular interactions (from here on: cellular networks) can reveal aspects of cellular function and overall molecular interaction behavior that cannot be described by other means. We will give here a brief introduction into the general logic of such network models and how we can gain novel, biologically, and medically relevant insights from applying them to the cancer context. This chapter describes network-based adaptive mechanisms that bring about the "creativity" of cancer cells to survive and expand in the unpredictable, often hostile, environments of tumor tissues. First, we describe the dominance shift from "business-as-usual" processes driven by the core of cellular molecular interaction networks to changes in the network periphery that lead to "creative" shortcuts between distant network regions and thus allow the network to respond to novel challenges.[1] This forms a general adaptation/learning mechanism that characterizes the initial stages of cancer development.[2] Such adaptive changes may change the topology of cellular networks from a rigid to a plastic state. Rigid networks have a dense core, disjunct modules (network groups), prominent hierarchy, low network entropy and so-called sink dominance. Rigid networks have only a few dominant attractors (i.e., stable states to where the network converges). Plastic networks have a fuzzy core, overlapping modules, less hierarchy/more loops, high network entropy, and source dominance. Plastic networks have many attractors, which are often dispersed. Alternating changes of network plasticity and rigidity help to encode novel information into the network structure, thus remodeling the network core and developing novel system attractors.[3] Cancer stem cells are characterized by exceptionally high evolvability involving rapid alternations between plasticity and rigidity.[4] Plastic and rigid networks (characterizing early and late-stage tumors, respectively) require conceptually different drug design strategies. Plastic networks (which dissipate stimuli very well) should only be attacked

with a "central hit," targeting hubs, bridges, and bottlenecks. If they were attacked at the network periphery, the effect of the drug would never reach the center of the network due to efficient stimulus dissipation. In contrast, rigid networks (which transmit stimuli without much dissipation) may become "overexcited" by "central hit" attacks, leading to unwanted side effects such as adverse drug reactions. Rigid networks require the "network influence drug design strategy" targeting the neighbors of their hubs and central nodes.[5] "Network influence targeting" of neighbors of key network nodes increases the precision of the intervention by targeting only certain functions of the key, neighboring network node. The chapter will conclude with the outline of network dynamics-based, personalized multitarget drug design strategies as a promising perspective for future therapies.

6.1 Network Science Provides Important Insights into Complex Cell Behaviors, Including Cancer

6.1.1 Definition of Cellular Networks

The term "cellular networks" encompasses many types of interaction networks inside a cell, such as protein-protein interaction networks (interactomes), signaling networks, gene transcription networks, and metabolic networks. Recently, additional types of intracellular networks have also been outlined, such as cytoskeletal networks, cellular organelle networks, and chromatin networks. However, currently we do not have enough information on most of these latter networks to include them into a detailed analysis of network adaptation processes of cancer cells.[6] Importantly, a rapidly emerging area of network science is the assessment of intercellular networks, which gives insight into the interactions of heterogeneous cancer cell types within the tumor, stromal cells, and immune cells.[7] The analysis of these networks has to date not yet yielded enough information to be included into this review, but their adaptation processes are an exceptionally interesting area of future study.

6.1.2 The Core-Periphery Learning Mechanism in Biological Systems

Three discoveries in the field of complex systems theory provided important insights into general adaptation mechanisms of complex systems.

a) Network core and periphery distinction. Starting with the work of Steve Borgatti and Martin Everett in 1999, a number of studies showed that most complex networks can be dissected down to a core and a periphery.[8] The network core refers to a central and densely connected set of a few network nodes, where connection density is often increased further by large edge (i.e., network node interaction) weights, which reflects the larger probability of the functional use of these interactions at the center of the network. In contrast, the network periphery consists of nodes that are noncentral, are sparsely connected, and attach preferentially to the core.[9] Importantly, some networks that have a

well-developed modular structure and small module overlap possess multiple cores, which correspond to the cores of their modules; such module cores can be defined by several algorithms.[10] Nodes of a network core are (evolutionarily) conserved and shielded from the environment of the network by the periphery.[11] Peripheral nodes are often sources of innovation, since they have a large degree of freedom (which is, for example, described in social networks as a lack of social pressure[12]).

b) Attractors of complex systems are deepened by learning. In 1969, Stuart Kauffman described that random genetic control networks develop a surprisingly small number of attractors.[13] Later studies of William Little, Gordon Shaw, and John Hopfield showed that attractors are deepened, or stabilized, during learning processes of networks of real or artificial neurons.[14]

c) Attractors of complex systems are encoded by core nodes of their network representation. Recent studies by Reka Albert, Bernold Fiedler, Atsushi Mochizuki, and their coworkers showed that attractors are encoded by overlapping node subsets of the strongly connected network region, which is the core of directed, bowtie networks.[15] These node subsets are both necessary and sufficient to determine the given attractor of the network.

6.1.2.1 The core-periphery learning theory

Based on the above three key observations and on several other studies described in Csermely,[16] the following general core-periphery learning theory for complex networks was conceived (figure 6.1). In most cases, a stimulus first affects peripheral nodes, since they are much more numerous than core nodes, and core nodes are often shielded by peripheral nodes from the network environment. The stimulus propagates then rapidly from the periphery to the core, since peripheral nodes are preferentially connected to core nodes. Once the stimulus signal has reached one node within the network core, it becomes rapidly shared/distributed throughout the entire core of the network by a fast process, since core nodes are densely connected, and their connecting edges (interaction paths) have a large weight, or "importance" or "preference," compared to other interactions (see the solid lines of figure 6.1).

After these initial steps, one of the following three scenarios may happen.[18]

Scenario 1. Activation of a previously encoded attractor. If the incoming stimulus had been experienced by the complex system several times before, a subset of core nodes has already formed a subgroup within the core that is even more densely interconnected than the rest of the core and also has already well-established connections with the "sensory" nodes of the periphery. This subgroup of network core nodes drives the complex system quickly to an attractor (outcome system response) that gives an adequate response to the formerly experienced stimulus. If now the same stimulus is repeated again, it is channeled immediately to this subgroup of core nodes, which drive the system to the very same attractor/response (figure 6.1A). This mechanism results in a fast, reliable, and robust response of the whole complex system.[19]

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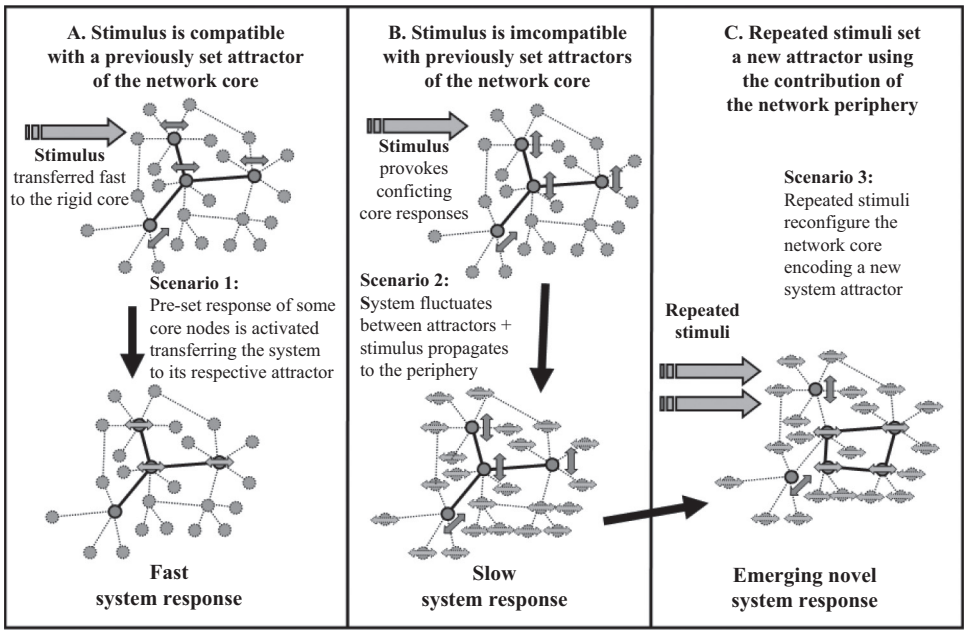

Figure 6.1
Description of the core-periphery learning mechanism of complex systems. (A) *Scenario 1*. The stimulus is rapidly channeled to the rigid core of the network (*dark gray nodes*) as a result of the central position of the core. It becomes "instantly" shared by core nodes due to their dense connections having large edge weights (*solid lines*). The stimulus (*large arrow*) is compatible with a previously set attractor of the complex system. This attractor is encoded by a subset of the core nodes (*top figure, two-headed arrows*) and provokes a fast, matching response (*bottom figure, two-headed arrows*), which rapidly dissipates the signal. (B) *Scenario 2*. The stimulus is incompatible with previously set attractors of core nodes (*highlighted*), provoking a fluctuation between attractors (*vertical two-headed arrows*). Consequently, the stimulus has enough time to spread back to the network periphery (*nonhighlighted nodes*), where it induces a slow, system-level, integrative response (*bottom figure horizontal two-headed arrows*). Here, a collective decision of the entire network emerges in a selection process of many, mostly stochastic steps (1). (C) *Scenario 3*. Repeated novel stimuli reconfigure the core (*highlighted nodes*) encoding a new system attractor (*horizontal two-headed arrows*). Reproduced with permission from Csermely.[17]

Scenario 2. Initial development of a new attractor. If the stimulus is a consequence of a novel, unexpected situation (figure 6.1B), it may be incompatible with any of the existing attractors encoded by the current core of the complex network. As a consequence, this novel stimulus may provoke conflicting core responses, inducing the complex system to fluctuate between its original attractors. This prolongs the time during which the stimulus cannot be dissipated by the system. During this extended period of time, the stimulus may have the chance to propagate back to the weakly connected peripheral nodes of the network, which form the majority of nodes in most networks and are not connected to each other, and therefore can only be accessed via the core. This process stabilizes the system (by modifying the position, size, saddles, or depth of the attractor basins in the

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complex system). The emergent periphery response is usually slow. This is partly because the reorganization of the periphery requires a large number of rather slow, mostly stochastic steps.[20] A key example of such a "learning step" of a complex system is the case of a "creative node,"[21] which has a dynamic position in the network (often acting as a "date hub"[22]), and creates a shortcut between previously distant network regions, allowing an entirely novel combination of the information previously encoded in these network regions.[23] In addition, the emerging system response is slow, because stimulus-driven periphery reorganization must often be attempted hundreds (if not thousands) of times before a new, adequate response is found.[24]

Scenario 3. Stabilization and encoding of the new attractor. In case the novel stimulus is repeated (many times), the peripheral network nodes, which were involved in "Scenario 2," may gradually reconfigure the network core adding nodes to it or exchanging its nodes (figure 6.1C). This process encodes the newly acquired response as a novel attractor of the system. Core reconfiguration may weaken or erase some of the earlier system attractors and thus may also serve as a "forgetting"/"erasure" mechanism.[25]

6.1.2.2 The core-periphery learning mechanism characterizes a wide range of complex systems

The core-periphery learning theory described above characterizes adaptation processes of a wide range of complex systems from protein structures to social networks.[26] In case of proteins, a rigid core is often surrounded by intrinsically disordered protein domains, which may become at least partially ordered during signaling processes when interacting with other proteins, hence forming a "conformational memory," which represents a learning process at the molecular level.[27] Individual cells may "learn" by the modification of signaling pathway dynamics and, most important, by developing epigenetic, chromatin memory.[28] (It will be a question of future studies whether these changes are initiated in the periphery of the signaling network and become part of its core.) Metabolic networks possess a reaction core containing all essential biochemical processes and have a large, adaptive periphery, which is switched on and off by transcriptional and regulatory processes driven by the flow of nutrients and emerging needs of the cell or by its environment.[29] In neuronal networks, peripheral nodes are becoming core nodes during the learning process. In social groups, "peripheral" individuals are not belonging to the social "elite," are free of social pressure, do not have the intrinsic need to maintain the "status quo," and thus may often become innovators. The collective action of peripheral (not well-connected) individuals is often called the "wisdom of crowds."[30]

6.1.2.3 The core-periphery learning theory applied to cancer

To date, we have already a number of good examples demonstrating that cell behaviors as described by the core-periphery learning theory may also drive the development of cancer. The following observations support this notion. Determinant nodes of the attractors of the epithelial-mesenchymal transition reside in the strongly connected region of the

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dynamic signaling network describing this process.[31] Expression patterns of the strongly connected region of microRNA-mediated intergenetic networks had an efficient prognostic potential for breast and colorectal cancer patients.[32] A recent study highlighted the importance of the first and second neighbors of cancer-related proteins in cancer development and their potential role in therapeutic approaches.[33] For example, this study could show that first neighbors of cancer-related (i.e., mutated or differentially expressed) proteins in interactomes and signaling networks have a degree of between-ness, centrality, and clustering coefficient at least as high as cancer-related proteins themselves, indicating a previously unknown central network position. Furthermore, there are 223 marketed drugs already targeting first neighbor proteins but applied mostly outside oncology, providing a potential list for drug repurposing against solid cancers.[34] It will be a task of further studies to prove or refute whether peripheral nodes of protein-protein interaction, signaling, or metabolic networks play a distinctive role in the development of novel responses of cancer cells to carcinogenic stimuli, stressful changes in the microenvironment, or cancer drugs.

6.1.3 Alternating Network Plasticity and Rigidity as a Hallmark of Cancer Cells

Complex systems often reside in one of two major configurations: either plastic or rigid. Plasticity and rigidity may be defined as a functional term of the complex system and as a structural term of the network description of the complex system. Functional and structural plasticity and rigidity are not describing the same phenomenon, but they largely correlate in their occurrence.[35] In the following, I will first introduce some general concepts concerning plastic and rigid networks and then give some examples of how these may apply to cancer.

6.1.3.1 Differences between functionally rigid and plastic complex systems

Functionally rigid systems have only few attractors, typically only one, and therefore have a very rough attractor landscape. (A rough attractor landscape means a set of attractors that are separated by large barriers.) A rigid object, such as a porcelain vase, is not able to change its state, unless it breaks, where this noncontinuous, nondifferentiable transition forms an entirely different system. In contrast, a functionally plastic system has a large number of attractors often associated with a smooth attractor landscape. (In a smooth attractor landscape, attractors are separated by very small barriers.) A plastic object, such as a paper clip, may adopt a large number of configurations, without an abrupt change. Consequently, rigid systems have a very poor adaptation (learning) potential, but they have an extremely good "memory" performing their dedicated task(s) with high precision and efficiency. On the contrary, plastic systems have an extremely good adaptation (learning) potential but have a very poor "memory," so they can perform specific tasks with only a low precision and efficiency.[36]

6.1.3.2 Differences between structurally plastic and rigid networks

Structurally plastic networks often have an extended, fuzzy core, where the network core cannot be easily demarcated and often contains most of the network nodes (instead of only a few). Plastic networks have fuzzy modules that also overlap to a large extent. Usually, plastic networks have little hierarchy, have more loops, and, if they have directionality, are source dominated. In contrast, structurally rigid networks have a small, dense core and disjoint, tightly organized, dense modules. Rigid networks are characterized by a strong hierarchy and, if they have directionality, by sink dominance (figure 6.2[37]). In summary, plastic networks are periphery dominated, while rigid networks are core dominated. This is in good agreement with the finding that network attractors are encoded by core nodes,[38] since the small and well-organized core of rigid networks encodes only a few attractors, where these attractors can be reached with a high probability and provide an optimized, highly efficient response. Plastic networks, on the other hand, have a large number of poorly defined attractors, which are encoded by a large number of poorly discriminated core nodes.

The novel stimulus, described in scenario 2 above, may "melt"/restructure part of the network core by decreasing the core edge weights. Note that this will also decrease the core rigidity, which leads to the destabilization of the original attractors and to an increase of learning potential to develop new attractors. Plastic network configurations can be induced and maintained by "soft spots," that is, nodes that are highly dynamic and have multiple, weak connections (figure 6.2). Note that these "soft spots" are the same as the "creative nodes" mentioned in scenario 2 above and are the ones that have a dynamic position in the network and can create shortcuts between previously distant network regions, allowing an entirely novel combination of nodes to encode the same information that was earlier already encoded in these same network regions.[44]

If the novel stimulus is repeated, as described in scenario 3 above, it may encode a novel set of constraints into the network structure, establishing a new region of the network core. This core extension makes the network more rigid again.[45] These rigid network configurations can be induced and maintained by "rigidity seeds," that is, nodes that increase the size of densely connected network clusters, for example, by completing a larger complete subgraph (i.e., clique, where every node is interacting with every other node) in the network or by joining two densely connected network regions (figure 6.2).

6.1.3.3 Alternating plasticity and rigidity is a general adaptation mechanism

Plastic-rigid transitions characterize a large number of complex systems from protein structures to social networks. An example of a protein-level alternation between plastic and rigid states are molecular chaperones that have an ATP (adenosine-tri-phosphate) hydrolysis-driven "chaperone-cycle," where they help the refolding of misfolded proteins by the physical extension of misfolded proteins, which is followed by their release from the chaperone cage. In their extended form, misfolded proteins become rigid, while after release, they are plastic again. If the misfolded protein folds to its native conformation, it

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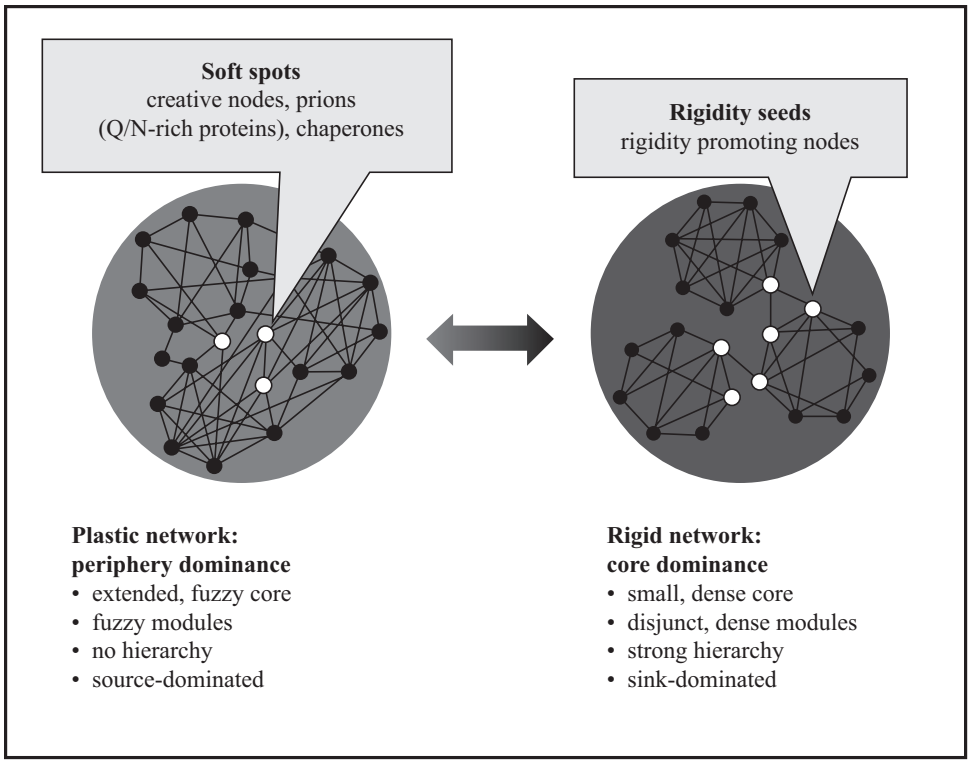

Figure 6.2
Properties of plastic and rigid networks. Network structures may adopt structurally plastic or rigid[39] network configurations. Plastic networks often have an extended, fuzzy core, where the network core cannot be easily discriminated and the core often contains most of the network nodes (instead of only a few). In addition, plastic networks have fuzzy modules with a large overlap. Usually, plastic networks display little hierarchy, have more loops, and, if they are directed, are source dominated.[40] In contrast, rigid networks have a small, dense core and disjoint, tightly organized, dense modules. Rigid networks are characterized by a strong hierarchy and, if they have directionality, by sink dominance.[41] In summary, plastic networks are periphery dominated, while rigid networks are core dominated. Plastic network configurations can be induced and maintained by "soft spots," that is, nodes that have highly dynamic and multiple, weak connections, such as creative nodes[42] exemplified by molecular chaperones, prions, or prion-like, Q/N-rich proteins.[43] In contrast, rigid network configurations can be induced and maintained by "rigidity seeds," that is, nodes that increase the size of densely connected network clusters, for example, by completing a larger complete subgraph (clique) in the network or by rigidly joining two densely connected network regions.

becomes more rigid, since it is stabilized in one conformation (attractor) instead of the competing many conformations (attractors) of the misfolded, at least partially disordered state. Such chaperone-driven extension-release (rigidity-plasticity) cycles iterate until the misfolded protein is refolded correctly again or becomes discarded by proteasomal degradation.[46]

Cell differentiation progresses via an initial "disorganization" phase of the gene expression networks in progenitor cells. This can be measured by (a) measuring the similarity

of gene expression profiles using symmetrized Kullback-Leibler distances, (b) applying a hierarchical clustering algorithm and calculating the giant component of the network, and (c) comparing the size of the giant component to that of the complete gene expression network. This final measure shows the level of organization of transcriptional processes. The initial "disorganization" is followed by the development of the much more "organized" gene expression network of the differentiated cell. In agreement with a transient increase of system plasticity during the cell differentiation process, the heterogeneity of the cell population increases considerably after the start of the differentiation process compared to the progenitor cells. As differentiation advances further, the heterogeneity of the cell population then markedly decreases, usually much below that observed within the progenitor cell population.[47] In addition, most terminally differentiated cells are highly specialized, which means they have often simple, hierarchical, rigid networks.

There are several other studies showing that plasticity-rigidity changes within neuronal networks can be observed during a large number of learning processes, such as bird song learning or infant speech learning. Human creativity consists of alternating "blind variation" and "selective retention" processes corresponding to more plastic and rigid neuronal states, respectively. Plasticity-rigidity cycles also characterize organizational learning processes.[48]

6.1.3.4 Plasticity-rigidity changes in carcinogenesis and cancer progression

The initial stages of cancer are characterized by an overall increase in network entropy of cellular networks[49] due to an increased number of stochastic processes (noise[50]) and loops,[51] as well as by increased phenotypic plasticity.[52] All these changes contribute to the increase of cellular phenotypic heterogeneity of cancer cells within a developing tumor (figure 6.3[53]). Higher-degree entropy of signaling networks was found to correlate with lower survival of prostate cancer patients.[54] A detailed investigation of normalized local and intermodular signaling network entropies revealed increased entropies in benign adenomas when compared to that of healthy colon epithelial cells. Importantly, colon carcinoma cells showed decreased entropies when compared to that of benign adenoma cells.[55] Similar changes showing transiently higher entropy were observed in early stage B-cell lymphoma and early hepatocellular carcinoma,[56] as well as in the more plastic, early stage proliferative phenotypes, compared to lower entropy levels in gene expression signatures of remodeling phenotypes of various late-stage cancer types.[57] This is a pattern of changes in system disorder remarkably similar to the one observed during cell differentiation.[58] Cells, which start from healthy attractors, develop during cancer initiation and progression a specific set of attractors, called "cancer attractors."[59] The change of the attractor landscape from the initially, relatively "rough" surface, which defines the healthy attractor(s), through a much "smoother" attractor landscape, where novel attractors arise and/or may become accessible, to the final stage of advanced tumors, where a well-developed and relatively stable set of cancer attractors becomes occupied and stabilized, corresponds very well to the observed increase and then decrease of signaling network entropy.[60]

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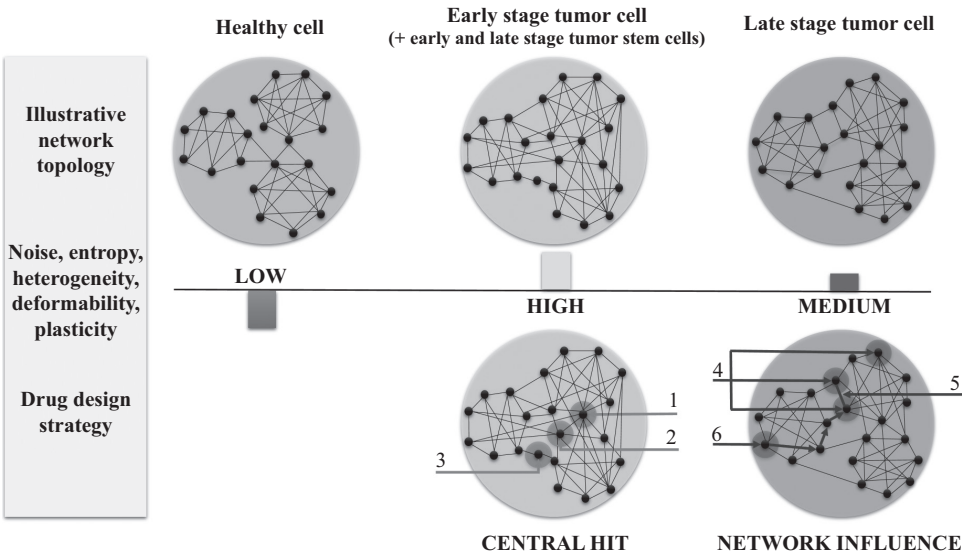

Figure 6.3
Conceptual summary: Cancer as an adaptation process of increasing and decreasing plasticity that requires corresponding, different drug-targeting strategies. The figure summarizes literature data[61] showing that cancer progresses by an initial increase of system plasticity followed by a late-stage decrease of plasticity. The plastic to rigid transition of network structure during cancer development requires distinctly different drug-targeting strategies in early versus late tumors. While at the early phase of carcinogenesis, central hits of hubs ("1"), intermodular bridges ("2"), or bottlenecks ("3") may be a winning strategy, at later stages of cancer progression, the more indirect means of a "network influence strategy," such as multitarget ("4"), edgetic ("5"), or allo-network drugs ("6"), should be used.[62] Unfortunately, most anticancer drug tests use cancer cell lines that have more plastic networks resembling those of the "early stage tumor-like" cells, while most patients are diagnosed with late-stage tumors with rigid cellular networks. Importantly, the heterogeneous cell populations of tumors may harbor early and late-stage cells at the same time.[63] Moreover, cancer stem cells may have the ability to change their plasticity from that of early to late-stage tumor cells and vice versa.[64] Therefore, multitarget, combinatorial, or sequential therapies using both central hit– and network influence–type drugs may provide a promising therapeutic modality. (Reproduced with permission from Gyurkó et al.[65])

6.1.3.5 Cancer stem cell–like cells display a high degree of evolvability of plasticity/rigidity changes

Cancer stem cells possess the capacity to self-renew and to repeatedly rebuild the heterogeneous lineages of cancer cells that comprise a tumor in a changing tumor microenvironment. They can assume both plastic and rigid network structures and cellular phenotypes. The plastic phenotype is rapidly proliferating and characterized by symmetric cell divisions. The rigid phenotype is characterized by not so frequent, asymmetric cell divisions and by increased invasiveness. A highly increased ability of plasticity modulation (which results in an increased level of evolvability) may prove to be a major discriminatory hallmark of cancer stem cells. In cancer development, cancer stem cells are repeatedly selected for high evolvability and become "adapted to adapt." Importantly, this increased plasticity modula-

tion ability may be a key reason why anticancer therapies often induce new cancer stem cells, instead of killing or transforming them. Such behavior was observed in non–small cell lung carcinoma after conventional chemotherapy (paclitaxel) or targeted therapies (Erlotinib) in breast cancer after taxane or anthracycline treatment or in hepatocellular carcinoma after carboplatin treatment. In these examples, network plasticity was increased by induction of specific transcription factors, such as Sox2 or Oct3/4, SRC, or IGFR signaling and epigenetic changes.[66]

6.2 Different Drug Design Strategies Are Required against Early and Late-Stage Tumors

Plastic and rigid networks require completely different drug-targeting strategies. Plastic networks have a rich and rather undifferentiated contact structure, which is able to dissipate "unexpected" external stimuli rather well. Drug treatment can be perceived as an "unexpected" intervention toward which the cancer cell has not developed an adequate response yet. Targeting noncentral nodes in a periphery-dominant plastic network would result in a fast dissipation of the intervention. Thus, plastic networks require a "central hit" that targets their central nodes, such as hubs, intermodular bridges, or bottlenecks (see labels 13 in figure 6.3, respectively). Rapidly dividing bacteria are typical examples of more plastic cellular networks. Not surprisingly, many antibiotics target central nodes of bacterial networks (with the notable exception of "choke point drugs," which target enzymes producing a key molecule for bacterial survival).[67] Rapidly proliferating cells of early stage cancers, as well as the rapidly proliferating, symmetrically dividing phenotype of cancer stem cells, have plastic networks, since the continuous changes of rapid cell division can be more adequately served by a contact-rich, noncentralized network structure. But it is also possible that rapid cell division is often a *consequence* of rapid changes in the tissue microenvironment that may initiate the switching to a plastic network structure; once network plasticity is increased, then more proliferation becomes possible as restrictive context is reduced. It can then become one further strategy to adapt by generating more cells that produce a microenvironment that supports cancer cell survival. Thus, "central hit"–type drugs may be more efficient against plastic phenotypes of cancer cells of early stage tumors. In agreement with the "central-hit" strategy, targets of anticancer drugs are often hubs.[68] Moreover, intermodular interactome hubs were found to associate more often with carcinogenesis than intramodular hubs.[69]

Rigid networks have a well-differentiated, centralized, hierarchical, modular structure, which is specialized to perform certain functions very efficiently. Rigid structures do not dissipate unexpected, random signals very well, since they were optimized for the rapid and efficient dissipation of only certain, previously experienced signals. As a consequence, rigid structures transmit signals rather well. This may cause rigid networks that are exposed to "central hits" to "overshoot," whereby not only the intended reaction but also unintended

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side effects may emerge. Cells forming a stable, cooperating community, such as cells of a tissue, have most of the time rigid networks. This makes the network influence strategy a key strategy in most diseases, such as diabetes or neurodegenerative diseases. As an example, the p62/SQSTM1 protein, which is a neighbor of raptor, the regulatory protein of mTOR (the mammalian target of rapamycin protein complex), is emerging as a novel target in both diabetes and cancer.[70] Late-stage tumors contain often "highly experienced cells," which have already been organized as a part of a community either in the original tumor or in metastases. The "overshoot" of "central-hit" targeting of cancer cells with rigid networks may result in the secretion of molecules that increase drug resistance of neighboring cells or cause necrosis instead of apoptosis, inducing various survival programs in their neighboring cells. Thus, instead of "central hits," the more indirect means of the "network influence strategy" should be used when targeting the rigid networks of late-stage tumors. The "network influence strategy" may target (first or second) neighbors of key network nodes.[71] Drugs for such a targeting method have been called "allo-network drugs" (label 6 in figure 6.3). This may allow the excitation of only a subset of the signaling pathways related to the central network node, which gives a much larger specificity to the intervention. (Such fine-tuning is close to impossible in extremely plastic networks, where the rich interaction structure channels the intervention to any direction, and thus the "fine-tuned" intervention becomes soon dissipated). "Network-influence targeting" may also be achieved by multitarget or combination therapies, which may use a combination of submaximum doses and may reach their goal by superimposing two (or more) actions at specific nodes of the network in a specific way, mobilizing again only a subset of the signaling pathways related to that particular node (label 4 in figure 6.3). Both neighbor-targeting and combination targeting may actually behave as "edgetic drugs" (label 5 in figure 6.3), which are targeting not an entire node but only one of its interactions, that is, one edge (interaction) of the signaling network. Edgetic targeting was used in the case of the superhub mTOR[72] or by inhibiting the p53/MDM2 connection by nutlins.[73] Neighbors of cancer-related proteins were found as widespread targets of drugs mainly used in diseases other than cancer and were suggested as candidates for potential repurposing efforts.[74] Several candidates for potential combination therapies were initially discovered by network-based identification.[75]

Most anticancer drug tests are currently performed on cancer cell lines, which are rapidly proliferating cells that have developed a plastic network, and from this point of view resemble more the phenotype of early stage tumors. Unfortunately, most patients are first diagnosed with late-stage tumors that have already more rigid cellular networks. Importantly, the heterogeneous cell populations of tumors may at the same time harbor cells that have both plastic and rigid networks.[76] Moreover, as described in the previous section, cancer stem cells have the ability to change their networks from a plastic to a rigid state and vice versa.[77] Cancer stem cells follow Nietzsche's proverbial saying "what does not kill me makes me stronger." Thus, conventional anticancer therapies may actually

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provoke cancer stem cell development.[78] In such scenarios, multitarget, combinatorial, or sequential therapies using both central hit– and network influence–type drugs may provide a more promising therapeutic modality.

6.3 Conclusions and Perspectives: Toward Personalized Drug Design Based on Insights from Network Science

This chapter introduced two key network-based cellular adaptation mechanisms that might play important roles in cancer. Both mechanisms modulate the evolvability of cancer cells to help their survival in an unpredictable tumor tissue environment. The first network-based adaptation mechanism is based on the "core-periphery learning theory."[79] Responses to previously experienced stimuli are encoded by node sets in the core of the network, while peripheral nodes are needed to "invent" novel responses to unexpected environmental changes. Thus, peripheral nodes are expected to play a major role in early stages of cancer development. Late-stage tumor cells may have already encoded several successful survival mechanisms into the core of their networks. The exploration of these ideas needs future studies. The second network-based adaptation mechanism was the alternation between plastic and rigid network states.[80] Alternating changes in network plasticity and rigidity help to encode novel information to the network structure by remodeling the network core and therefore developing novel system attractors. Cancer stem cells utilize this mechanism to develop and maintain an exceptionally high evolvability.[81]

Importantly, plastic and rigid networks (mainly characterizing early and late-stage tumors[82]) require conceptually different drug design strategies. Plastic networks require "central hits" targeting their hubs, bridges, and bottlenecks. On the contrary, rigid networks require the "network influence drug design strategy" targeting the neighbors or edges of their hubs and central nodes.[83]

Although the above suggestions have been formulated as a result of integrating a number of individual experimental studies listed in references 1 through 6, they require further experimental evidence to establish their precise limits and possibilities. A few of these important areas of future research are as follows:

1. Further studies are needed to characterize the core-periphery mechanism and plastic/rigid alternations of progressing cancer cell and cancer stem cell networks.
2. Systematic studies must show differences in the efficacy of targeting various network positions in early and late-stage tumors.
3. Systemwide studies (such as total gene expression/complete exome data preferably at single cell level) are needed to clarify the network consequences of multitarget, combinatorial, or sequential targeting therapies.
4. The above areas require extension to intercellular network interactions as to date only a few studies have been performed.[84]

5. Both intra- and intercellular networks may be "personalized" and/or "localized," taking into account the location of the hosting cells within the tissue, building in the functional (e.g., signaling) consequences of the specific profile of mutations and epigenetic changes of the given tumor and subsequent modification of network nodes and edges according to the transcriptome and proteome of the given tumor. Importantly, due to the heterogeneity of tumors and the complexity of chromatin modifications, this task may be much more complex than initially thought.

6. Last but not least, most of the above considerations involved mainly structural changes of cellular networks and have not taken into account the dynamic analysis of cellular networks in order to determine, predict, and modify the changes in their attractor landscape structure. Several important recent studies[85] have established the novel area of "cancer attractor redesign." The aim of such approaches is to develop multitarget drugs and drug combinations, which (a) do not allow the dominance of proliferation, invasiveness, and so on attractors of cancer cells; (b) act as "differentiation therapies" guiding cancer cells back to their healthy attractors[86]; and (c) might lock cancer stem cells into their plastic or rigid phenotype.

The author is very optimistic that a paradigm shift is about to emerge that will lead to a change in the design strategies for anticancer therapies, such that the primary goal will be cancer cell "reeducation" and guidance toward the healthy state, instead of their mass murder, a strategy that does not work so well, as many decades of clinical outcome data have shown. The emerging knowledge on network adaptation mechanisms in complex molecular interaction networks will certainly be very useful in guiding and driving these efforts. From a network science perspective, it is quite clear that simplistic, linear, mutation-centric concepts, such as looking for "the" cancer genes and/or mutations, cannot solve the entire puzzle of successful cancer therapies. Such a "systems view of cancer" requires novel strategies that have to be drastically different from the current "mutation fishing" approaches. The author hopes that complex network theory and its applications, presented in this chapter, will contribute to a systems-level understanding of cancer and to the development of system-based anticancer therapies.

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Notes

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Rethinking Cancer

A New Paradigm for the Postgenomics Era

Edited by Bernhard Strauss, Marta Bertolaso, Ingemar Ernberg, and Mina J. Bissell

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Preface

This book is published at an important juncture in the history of cancer research. Never before have we known so much about the individual cancer cell, yet never before has it been so unclear how to translate this knowledge into treatment success. This book is also published over a year into the global COVID-19 pandemic. Apart from its many other devastating consequences, the pandemic has caused many millions of cancer patients to have not been treated or diagnosed. Moreover, cancer research spending has dropped significantly. In October 2020 the UK's National Cancer Research Institute released figures projecting a 24 percent drop in the UK's overall cancer research spending, driven by a 46 percent fall in charity sector funding. The impact of the pandemic on cancer patients and cancer research will be felt for years to come, and will make it all the more important to determine what to focus on with the funds available.

Great technological progress over the past four decades has enabled earlier diagnosis, better surgery, disease monitoring, and follow-up, and it just begins to show in the cancer survival statistics. What is still hard to show is any significant extension of life span after treatment of late-stage disease, the real measure of our ability to effectively cure cancer. This is urgently needed, however, in the face of a worldwide, rapidly increasing cancer incidence. It seems that we are still waiting for the progress that was promised at the time of the "genomics revolution" by the sequencing of the first human genome twenty years ago.

The early 2000s were a time of great optimism in biomedical research, as it was generally assumed that once we know every single human gene, applications would be easy to engineer, and tangible benefits for human health would inevitably follow. But cures based on this "complete" knowledge of our genetic blueprint have remained largely elusive. Targeted therapy, as in precision cancer medicine (PCM), is still only applicable to small subsets of patients, and treatment outcomes are often not as expected. Cancer immunotherapy, after fifty years of basic research, could finally be translated into clinical practice during the last decade, but is so far successfully applicable to only a few types of cancer. Over the same time span, precise manipulation of the genome has become even easier than anybody would have thought back then. In addition, novel computational methods have enabled in-depth analysis of vast amounts of genomics data, be it at the single cell or tumor level, or in large

cohorts of cancer patients, with the aim to uncover the genes and molecular pathways that cause cancer. The genomics era was characterized by a sense of relief, as one was under the impression that finally the protocol for understanding and manipulating life had truly arrived. It appeared that with a few minor technical optimizations, any problem in biology, including in humans, would become solvable, at least "in principle."

In the second decade of the twenty-first century, however, it has become clear that simple correlations between genes, mutations, and cancer that have diagnostic or therapeutic value are not to be found exclusively at the DNA sequence level. It seemed that we had reached "peak genomics." Even among cancer systems biologists, consensus started to build that understanding cancer as a perturbation in a complex multimodal, molecular network will not lead to straightforward actionable treatments, despite impressive recent advancements in computational powers and single-cell analysis methods. What these approaches have uncovered instead is enormous heterogeneity at the genomic level, often presented as "complexity": not only between different cancers but also of the same cancer type in different patients, and even between the individual cancer cells within a single tumor in one patient. This ubiquitous observation has led to the declaration of a "complexity crisis" in the cancer genomics field. On the one hand, this admission has relativized the significance of the large amounts of cancer data that have been accumulated and was often used to explain the failures of new cancer drugs in the clinic; on the other hand, the implicit understanding was that doubling down on the acquisition of DNA sequence data and on throughput of analysis (using artificial intelligence) will lead to important breakthroughs in the foreseeable future.

Despite the persistence of the central causal narrative in cancer biology, which holds that cancer is caused by mutations in certain genes, many researchers have begun to doubt that DNA-level information is sufficient for understanding the cancer phenotype and have moved on to cancer epigenomics and other kinds of -omics. Hence, there is now widespread commentary about the arrival of the "postgenomics era" in cancer research. Originally, this term had an optimistic connotation, supposed to mean that things will be easier from then on, say with the ability to personalize treatments, and to tailor therapies to the exact specifications of a patient's disease. Although indeed technically achievable, it now appears very unlikely that these approaches can ever become standard of care due to their enormous complexities and thus inevitable diagnostic and therapeutic uncertainties, not to mention the high costs of the methodologies involved. Meanwhile, data on the success rates of "targeted" drugs based on genomic information show that these drugs have overall been far less successful in the clinic than expected.

Perhaps, "postgenomics" really is meant to announce a reboot: we have tried genomics, with only modest success in curing cancer, and now need to move on to something else—but where to? This is what this book is about.

Applying loosely a historical framework as presented by Thomas S. Kuhn in his 1962 book *The Structure of Scientific Revolutions*, it appears that an increasing number of scientists would agree today that the current consensus that defines what is considered

"normal science" in cancer research, or its contemporary scientific "paradigm" in Kuhn's terminology, has been insufficient to answer basic questions about carcinogenesis.

Emerging from this wider historic perspective and from the very concrete results of our own scientific work and that of others, the following two premises motivated the creation of this volume:

1) The current paradigm, namely that a number of specific genes, when mutated or misregulated, cause cancer, has not by itself led to a cure for cancer—a failure clearly not due to lack of financial investments or intellectual effort. Therefore, a new theoretical framework for causally understanding and treating cancer is required. (We are not criticizing the general understanding of how genes function and their causal role in biology.)

What went wrong? We believe that first and foremost, we have applied an incomplete or incorrect theoretical framework in our attempts to explain carcinogenesis. This concerns specifically how a simplistic understanding of the causal role of individual genes has been applied to cancer.

2) Several lines of evidence, supported by comprehensive data over the past two decades, can be identified that challenge the current paradigm. These are now converging toward a more widely accepted systems view of cancer and are presented in this volume along different "dimensions" of cancer. This view has, however, not yet led to a change in research practices or to fundamentally new experimental approaches in mainstream cancer research.

At the core of this premise is the understanding that models of linear causation, based on single (mutated) genes or networks thereof, "in principle" cannot explain the cancer phenotype and therefore cannot be used to formulate a cure. This view is now increasingly supported by the very data that were initially collected with the aim to find simple answers. However the logical structure of most current cancer research efforts still appears to follow a mind-set that wants to find *the* few most relevant cancer genes for a given tumor or *the* corresponding drug that targets such genes in a precise manner—while it is becoming more and more obvious that cancer is certainly more complex than that. To change this mind-set, we believe, requires active concerted efforts in order to translate alternative concepts into scientific practice—instead of waiting for "linear" science to take its course, while hoping that the relevant breakthroughs will emerge eventually "anyway." From the patients' perspective, that is certainly not good enough value for research money.

This volume aims to reemphasize the point that it is primarily novel conceptual or theoretical thinking that is required to drive progress in cancer research. Ultimately, only a clearly detectable change in research practices and funding policies will tell whether new thinking has arrived. New thinking becomes particularly important as currently, an increasing number of formerly "solid" fundamental concepts that are still constituting elements of the current paradigm, such as "oncogene," "clonal expansion," "tumor suppressor gene," and "driver mutation," to name a few, are becoming increasingly "softened" and attached with

various disclaimers regarding their explanatory power, often by the very scientists who introduced them earlier. It seems therefore rather surprising that this has not led to a frantic search for additional conceptual building blocks, if not new frameworks.

This highlights also one central issue with theoretical thinking in cancer research: the fact that novel concepts emerge mainly in the basic sciences where they can be dynamic and evolving, but cancer clinicians remain suspended in the tension between their own empirical insights based on clinical practice and the concepts from the basic sciences they apply (usually with some delay) to the cancer context in humans. When clinical outcomes are not in agreement with the prevailing paradigm, for instance, when no plausible "cancer mutations" are found in a tumor, or rationally designed, target-selective drugs do not work as expected or even make the tumor more aggressive, then clinicians usually assume that the principles established in cell culture, animal models, or small cohorts may not apply, because humans might be just too complex and too diverse. They would certainly not question the scientific foundations that guide clinical practice, let alone assume flaws therein that needed addressing. Despite the fact that the number of clinician-scientists (MD-PhDs) is increasing, and integration between clinical and basic sciences is steadily improving, it seems by now quite clear that beyond such logistical advancements, theory-driven cancer biology needs to lead the way with conceptual innovation.

Over the past four decades, the dedication to explain cancer exclusively from the gene level up has been so all-encompassing that even trying to conceptualize alternative ideas has become difficult for at least two generations of cancer scientists. It has also discouraged research into other causally relevant processes beyond the single cancer cell level, depriving us of not only the theoretical but also the experimental tools to study them. But where do we start if we are to create a new theory framework, and what would its conceptual building blocks be?

Here we have gathered contributions from a number of theory-minded cancer scientists who present ideas and results that are covering many different aspects of cancer but are united by the view that it is paramount to revise the current somatic mutation paradigm if we are to make more progress in finding a cure for cancer. Their thinking comes from different areas of basic cancer cell biology, clinical research, and theoretical investigation, but they share a systemic and dynamic understanding of cancer that goes well beyond the idea that specific mutations in certain genes cause cancer and that assembling them into linear schemes of causation would be sufficient to explain carcinogenesis.

We are aware that this volume had to remain incomplete, as many colleagues who have contributed over the years with their work and theoretical thinking to a possibly emerging new paradigm could not be included here because of time and space constraints. In particular, the areas of inflammation and cancer immunology, two of the most dynamic fields in recent cancer research, are not explicitly represented, although references to relevant findings in these areas are made repeatedly by contributing authors throughout the book.

We believe that not only has sufficient solid evidence accumulated to warrant a change of the current paradigm based on scientific reasoning, but also that over the past decade the readiness for change has increased within the scientific community—despite the fact that funding agencies and mainstream research efforts still largely adhere to outdated concepts.

In this volume, we do not argue yet another critique of current research practices as this has been done by some of the authors and others in the past. Instead, we wish to present a number of conceptual stepping-stones that should lead the reader to a new vantage point from where a coherent new theory framework for cancer research might become visible.

The editors