In: Bernhard Strauss, Ingemar Ernberg, Mina Bissell (Eds.) Cancer Theory. MIT Press, in press

Adaptation of cancer cell networks

Peter Csermely

This chapter will describe network-based adaptive mechanisms, which mobilize the 'creativity' of cancer cells to survive and expand in an unpredictable environment. First, the dominance-shift from 'business-as-usual' processes driven by the core of cellular networks to changes in the network periphery leading to 'creative' shortcuts between distant network regions and answering novel challenges (1,2) will be described. This forms a general adaptation/learning mechanism and 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, hierarchy, small network entropy and sink-dominance leading to a few attractors. Plastic networks have a fuzzy core, overlapping modules, less hierarchy/more loops, large network entropy and source-dominance leading to many attractors. Alternating changes of network plasticity and rigidity help to encode novel information to the network structure remodeling the network core and developing novel system attractors (2,3). Cancer stem cells are characterized with exceptionally large evolvability involving rapid alternations in their plasticity and rigidity (4). Plastic and rigid networks (characterizing early- and late-stage tumors) require conceptually different drug design strategies. Plastic networks (which dissipate stimuli very well) should only be attacked by a "central hit" targeting their hubs, bridges and bottlenecks, since if they are attacked at their network periphery, the effect of the drug will never reach the center of the network due their efficient dissipation. On the contrary, rigid networks (which transmit stimuli without a large dissipation) may be 'over-excited' by "central hit" attacks, leading to side-effects. Rigid networks require the "network influence drug design strategy" targeting the neighbors of their hubs and central nodes (5-8). "Network influence targeting" of neighbors of key network nodes increases the precision of intervention 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 of future therapies.

Definition of cellular networks. In this chapter I will describe the adaptation mechanisms of ‘cellular networks’. Primarily, the term ‘cellular networks’ contains many types of networks inside a cell, such as protein-protein interaction networks (interactomes), signaling networks, gene transcription networks and metabolic networks. Recently, additional types of intra-cellular 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 get them included to a detailed analysis of network adaptation processes of cancer cells (5,9-11). Importantly, a rapidly emerging area of network science is the assessment of inter-cellular networks, which gives insight to the interactions of heterogeneous cancer cell types in the tumor, stromal cells and immune cells (12-14). The analysis of these networks has not resulted yet enough information to get them included to the current review, but their adaptation processes give an exceptionally interesting area of future studies.

The core-periphery learning mechanism and it role in cancer development

Three discoveries gave important insight to the mechanism of complex systems' adaptation.

A.)Network core and periphery. Starting with the work of *Steve Borgatti* and *Martin Everett* in 1999 (15) a number of studies showed that most networks can be dissected to a core and a periphery. 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 weights. In contrast, the network periphery consists of nodes that are non-central, sparsely connected, and attach preferentially to the core (16). Importantly, some networks (where the modular structure is well-developed, and the network modules have a relatively small overlap) possess multiple cores, which correspond to the cores of their modules. Module cores can be defined by several algorithms (17,18). Nodes of network core are (evolutionarily) conserved and shielded from the environment of the network by the periphery (16). Peripheral nodes are often sources of innovation, since they have a large degree of freedom (which is described in social networks as a lack of social pressure; 16).

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 (19). Later studies of *William Little*, *Gordon Shaw* and *John Hopfield* showed that attractors are deepened during the learning process (20-22).

C.) Attractors of complex systems are encoded by core nodes of their network representation. Recent studies of *Reka Albert*, *Bernold Fiedler*, *Atsushi Mochizuki* and their co-workers showed that attractors are encoded by overlapping node subsets of the strongly connected network component, which is the core of directed, bow-tie networks (23-26).

The core-periphery learning theory. From the above three key observations and from several other studies described in Ref. 2 the following core-periphery learning theory was conceived (Figure 1). In most cases the stimulus is affecting 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 from the periphery to the core in a fast process, since peripheral nodes are preferentially connected to core nodes. Once the stimulus reached one node within network core it becomes shared by the whole core of the network in a fast process, since core nodes are densely connected, and their connecting edges have a large weight (see the solid lines of Figure 1).

After these starting steps one of the following three scenarios may happen (2).

Scenario 1. Activation of a previously encoded attractor. If the incoming stimulus had been experienced by the complex system several times before, a set of core nodes have already formed a sub-group of the core which is even more densely interconnected than the rest of the core. This sub-group of nodes drives the complex system to an attractor giving an adequate response to the formerly experienced stimulus. If now the same stimulus is repeated again, it is channeled to this sub-group of core nodes, which drive the system to the very same attractor (Figure 1A). This mechanism results in a fast, reliable and robust response of the whole complex system (2).

Scenario 2. Initial development of a new attractor. If the stimulus is a consequence of a novel, unexpected situation (Figure 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 when the stimulus has not been dissipated by the

system yet. During this extended 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 which are not connected to each other, therefore can only be accessed via the core. This process stabilizes the system. and may modify the position, size, saddles or depth of the complex system's attractor basins. The emergent periphery-response is usually slow. This is partly because the re-organization of the periphery is requiring a large number of rather slow, mostly stochastic steps (2). A key example of such a 'learning step' of a complex system is the case of a 'creative node' (1), which has a dynamic position in the network (often acting as a 'date hub'; 17,27), and makes a shortcut between previously distant network regions allowing an entirely novel combination of the information encoded in these network segments previously (1). In addition, the emerging system response is slow because stimulus-driven periphery reorganization must often be attempted hundreds (if not thousands) of times before finding a new, adequate response (2).

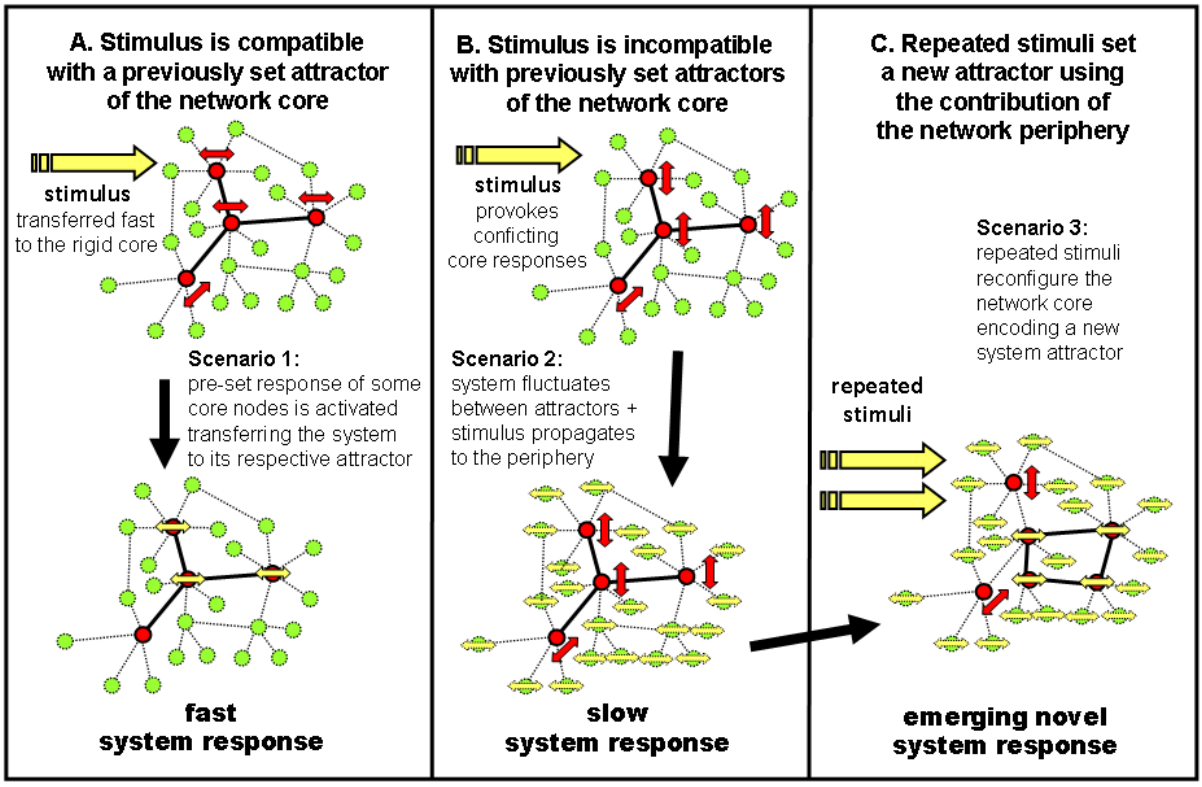

Figure 1. Description of the core-periphery learning mechanism of complex systems. The stimulus is rapidly channeled to the rigid core of the network (*red nodes*) as a result of the central position of the core (2). It becomes 'instantly' shared by core nodes due to their dense connections having large edge weights (*solid lines*). Panel A: *Scenario 1.* The stimulus (*yellow arrow*) is compatible with a previously set attractor of the complex system. This attractor is encoded by a subset of the core nodes (*horizontal red double arrows*) and provokes a fast, matching response (*solid line yellow double arrows*), which dissipates the signal in a rapid process. Panel B: *Scenario 2.* The stimulus is incompatible with previously set attractors of core-nodes (*red*) provoking a fluctuation between attractors (*red double arrows*). Consequently, the stimulus has enough time to spread back to the network periphery (*green nodes*), where it induces a slow, system-level, integrative response (*dashed line yellow double arrows*). Here, a collective decision of the entire network emerges in a selection process of many, mostly stochastic steps (1). Panel C: *Scenario 3.* Repeated stimuli reconfigure the core (*red nodes*) encoding a new system attractor (*solid line yellow double arrows*). Reproduced with permission from Ref. (2).

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 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' mechanism (2).

The core-periphery learning mechanism characterizes a wide range of complex systems. The core-periphery learning theory, described above characterizes the adaptation of a wide range of complex systems from protein structures to social networks (2). In case of proteins the rigid core is often surrounded by intrinsically disordered protein segments, which may become at least partially ordered during signaling processes forming a 'conformational memory' which helps a learning process at the molecular level (2,28). Individual cells may 'learn' by the modification of signaling pathway dynamics (29), and – most importantly – by developing epigenetic, chromatin memory (30). 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 its environment (31). In the last few years a large number of publications showed the validity of the core-periphery learning theory in neuronal and social networks. In social groups 'peripheral' individuals A.) are not belonging to the social 'elite'; B.) are free of social pressure; C.) do not have the intrinsic need of maintaining the 'status-quo'; D.) and thus may often become innovators. The collective action of peripheral individuals is often called as the "wisdom of crowds" (2).

Validity of the core-periphery learning theory in cancer: initial observations and an area of further studies. There are only a few sporadic examples yet, showing the possibility that the core-periphery learning theory may also drive the development of cancer. Determinant nodes of the attractors of the epithelial-mesenchymal transition reside in the strongly connected component of the dynamic signaling network describing this process (32). Expression pattern of the strongly connected component of miRNA-induced inter-genetic networks had an efficient prognostic potential for breast and colorectal cancer patients (33). A recent study highlighted the importance of the first and second neighbors of cancer-related proteins in cancer development and potential therapeutic approaches (8). 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.

Alternating plasticity and rigidity as a hallmark of developing cancer cells

Complex systems often reside in one of two major configurations: 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 (obviously) not describing the same phenomenon but they largely correlate in their occurrence (3,34).

Differences of functionally rigid and plastic complex systems. Functionally rigid systems have only a very few attractors, typically only one, having a very rough attractor landscape. (A rigid object, like a needle is not able to change its state, unless it breaks, where this non-continuous, non-differentiable transition forms an entirely different system.) On the contrary,

a functionally plastic system has a large number of attractors often associated with a smooth attractor landscape. (A plastic object, like 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 (3,34).

Differences of plastic and rigid networks. Structurally plastic networks often have an extended, fuzzy core, where the network core can not be easily demarcated and often contains most of the network nodes (instead of only a few). Plastic networks have fuzzy modules having a large overlap. Usually plastic networks display a low hierarchy, have more loops and, if they are directed, they are source-dominated. On the contrary, 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 are directed, by sink-dominance (Figure 2; 3,34,35). In summary, plastic networks are periphery dominated, while rigid networks are core-dominated. This is in a good agreement with the findings that network attractors are encoded by core-nodes (23-26), 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. On the contrary, plastic networks have a large number of poorly defined attractors, which are encoded by a large number of poorly discriminated core nodes.

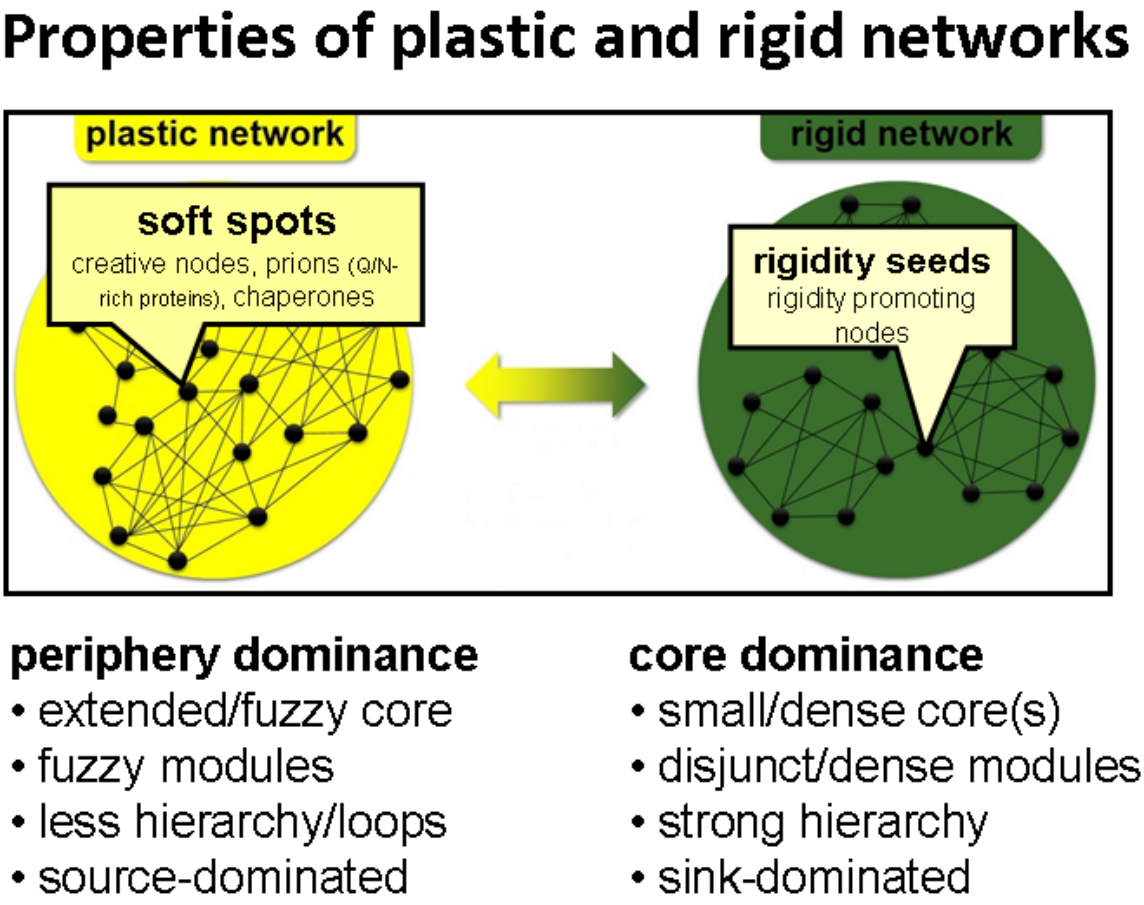

Figure 2. Properties of plastic and rigid networks. Network structure may adopt structurally plastic and rigid (3,34) network configurations. Plastic networks often have an extended, fuzzy core, where the

network core can not 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 having a large overlap. Usually plastic networks display a low hierarchy, have more loops and, if they are directed, they are source-dominated (35). On the contrary, rigid networks have a small, dense core and disjoint, tightly organized, dense modules. Rigid networks are characterized by a strong hierarchy and, if they are directed, by sink-dominance (35). In summary, plastic networks are periphery dominated, while rigid networks are core-dominated. Plastic network configurations can be induced and maintained by 'soft spots', i.e. nodes which have a high dynamics and multiple, weak connections such as creative nodes (1) exemplified by molecular chaperones, prions or prion-like, Q/N-rich proteins (1,28). On the contrary, rigid network configurations can be induced and maintained by 'rigidity seeds', i.e. nodes which increase the size of densely connected network clusters, e.g. by completing a larger complete subgraph (clique) in the network or by joining two densely connected network regions.

The mismatched stimulus, described in "Scenario 2" before, may ‘melt’ 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 an increase of learning potential to develop new attractors. Plastic network configurations can be induced and maintained by 'soft spots', i.e. nodes which have a high dynamics and multiple, weak connections (Figure 2). Note that these 'soft spots' are the same as the 'creative nodes' (1) mentioned in "Scenario 2" above, which have a dynamic position in the network and make a shortcut between previously distant network regions allowing an entirely novel combination of the information encoded in these network segments previously (1).

If the mismatched stimulus is repeated, as described in "Scenario 3" before, it may encode a novel set of constraints to the network structure establishing a new segment of the network core. This core-extension makes the network more rigid again (3,34). These rigid network configurations can be induced and maintained by 'rigidity seeds', i.e. nodes which increase the size of densely connected network clusters, e.g. by completing a larger complete subgraph (clique) in the network or by joining two densely connected network regions (Figure 2).

Alternating changes of plasticity and rigidity form a general adaptation mechanism. Plastic-rigid transitions characterize a large number of complex systems from protein structures to social networks. As an example of the protein-level changes, molecular chaperones have an ATP 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 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 follow each other until the misfolded protein is refolded again or becomes discarded by proteasomal degradation (3).

Cell differentiation proceeds via an initial 'disorganization' of the gene expression networks of the progenitor cells. This can be measured by the size of the largest cluster as compared to that of the complete gene expression network. 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 becomes much larger after the start of the differentiation process than that of the progenitor cells. As the differentiation proceeds, the

heterogeneity of the cell population markedly decreases, usually much below to that observed with the progenitor cells (36).

There are several other studies showing that plasticity-rigidity changes of 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 (3).

Plasticity-rigidity changes in cancer development. The development of cancer is characterized by an increase in the network entropy of cellular networks (37-40) by an increased level of stochastic processes (noise; 41), by an increased amount of loops (42) and by increased phenotypic plasticity (4,6,43). All these changes contribute to the increase of cellular heterogeneity of cancer cells in a developing tumor (Figure 3; 44-54). Higher degree-entropy of signaling networks was found to correlate with lower survival of prostate cancer patients (39). A detailed investigation of normalized local and inter-modular signaling network entropies revealed increased entropies in adenoma when compared to that of healthy colon epithelial cells. Importantly, colon carcinoma cells showed decreased entropies when compared to that of adenoma cells (40). Similar changes were observed by the transiently larger entropy of early stage B cell lymphoma and hepatocellular carcinoma development (45,46), as well as by the more plastic proliferative phenotype than that of the remodeling phenotype in gene expression signature analysis of various cancer types (47). This shows a remarkably similar pattern of changes in system disorder than that observed during cell differentiation (36). Cells, which start from their healthy attractors, reach a specially developed set of attractors, called "cancer attractors" (48-51) during cancer development. The change of the attractor landscape from the starting, relatively 'rough' surface, which defines the healthy attractor(s) well, 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 (40) of signaling network entropy.

Cancer stem-like cells display especially large evolvability of plasticity/rigidity changes. Cancer stem cells (i.e. cells within a tumor that possess the capacity of self-renew and to repeatedly re-build the heterogeneous lineages of cancer cells that comprise a tumor in a new environment) may possess both plastic and rigid network structures and cellular phenotypes. The plastic phenotype is rapidly proliferating and characterized by symmetric cell division. 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 became “adapted to adapt”. Importantly, this increased plasticity modulation ability may be a key reason why anti-cancer therapies often induce cancer stem cells instead of killing or transforming them (4,6,55-57).

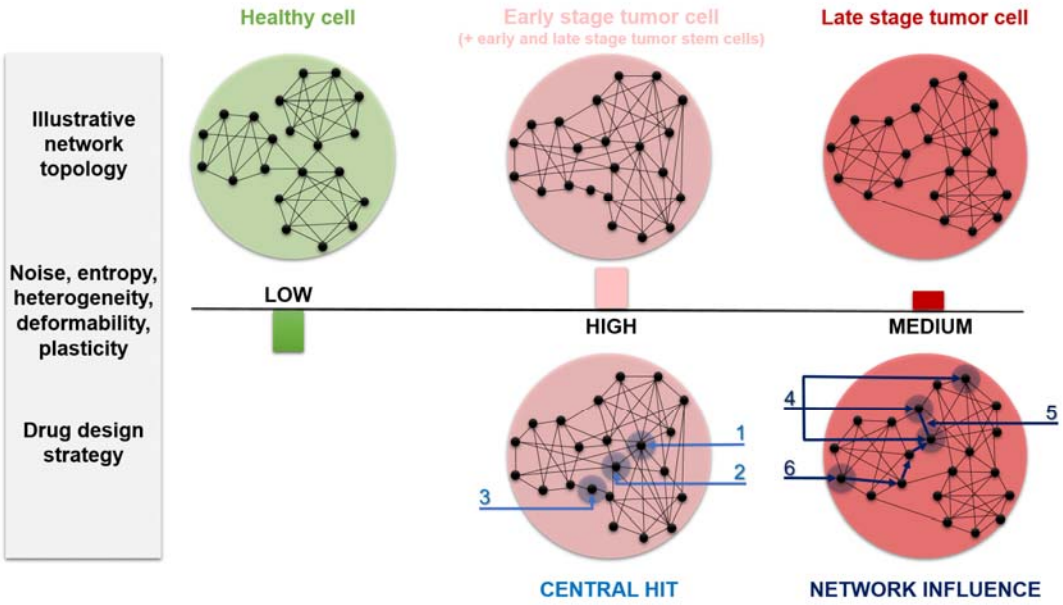

Figure 3. Conceptual summary: Development of cancer as an adaptation process of increasing and decreasing plasticity defining different drug targeting strategies. The figure summarizes literature data (6, 37-51) showing that cancer progresses by an initial increase of system plasticity followed by a late-stage decrease of plasticity. The more plastic to more rigid transition of network structure during cancer development requires a rather different drug targeting strategy in early and late tumors. While at the early phase of cancer development "central hits" (5) of "1" hubs, "2" inter-modular bridges, or "3" bottlenecks may be a winning strategy, at later stages of carcinogenesis the more indirect means of "network influence strategy" (5), such as "4" multi-target (52), "5" edgetic (53) or "6" allo-network drugs (54) should be used. Very unfortunately, most anti-cancer drug tests use cancer cell lines which have more plastic networks resembling to those of the "early stage tumor like" cells, while most patients are diagnosed having late stage tumors with rigid cellular networks. Importantly, the heterogeneous cell populations of tumors (44) may harbor early- and late-stage cells at the same time. Moreover, cancer stem cells may have the ability to change their plasticity from that of early- to late-stage tumor cells and vice versa (4). Therefore, multi-target, combinatorial or sequential therapies using both central hit- and network influence-type drugs may provide a promising therapeutic modality. Reproduced with permission from Ref. (6).

Drug design strategy differences against early 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. Note that drug treatment can be perceived here as an 'unexpected' intervention towards which the cancer cell has not developed an adequate response yet. Targeting non-central nodes in the a periphery-dominant plastic networks would result in a fast dissipation of the intervention. Thus plastic networks require a "central-hit", which targets their central nodes, such as hubs, inter-modular bridges or bottlenecks (see numbers "1" through "3" of Figure 3, respectively). Rapidly dividing bacteria are typical examples of more plastic cellular networks. Not surprisingly many antibiotics (with the notable exception of "choke point drugs", which target enzymes producing a key molecule for bacterial survival) target central nodes of bacterial networks (5). 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, non-centralized network structure. Thus, "central-hit" type drugs may be more efficient against plastic phenotypes of cancer cells, such as that of early stage tumors. In agreement with the "central-hit" strategy, targets of anticancer drugs are often hubs (58). Moreover, inter-modular interactome hubs were found to associate with oncogenesis better than intra-modular hubs (59).

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 have been optimized to the rapid and efficient dissipation of only certain, previously experienced signals. As a consequence, rigid structures transmit signals rather well. This may make "central-hits" an 'overshoot', where not only the required action but also side effects may develop. 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 e.g. diabetes or neurodegenerative diseases (5). Late stage tumors have 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 in case of cancer cells having rigid networks may result in the secretion of several molecules helping the resistance of neighboring cells, or 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" (5) 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 (8). Such a targeting method has been called as "allo-network drugs" (54; number "6" of Figure 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 contact structure channels the intervention to any direction, thus the 'fine-tuned' intervention becomes soon dissipated.) "Network-influence targeting" may also be reached by multi-target or combination therapies, which may use suboptimal 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 (52; number "4" of Figure 3). Both neighbor-targeting and combination targeting may actually behave as "edgetic drugs" (53; number "5" of Figure 3), which are targeting not an entire node, but only one of its interactions, i.e. an edge of the signaling network. Edgetic targeting was used in case of the super-hub mTOR (60) or inhibiting the p53/MDM2 connection by nutlins (61). Neighbors of cancer-related proteins were found as wide-spread targets of drugs used in diseases mostly other than cancer, and were suggested as targets of potential re-purposing efforts (8). Several initial network-based identification of potential combination therapies have been published (5, 62-64).

Most anti cancer drug tests are performed on cancer cell lines, which are rapidly proliferating cells having a plastic network and from this point of view resemble to the cells of early stage tumors. Very unfortunately, most patients are diagnosed with rather late stage tumors having more rigid cellular networks. Importantly, the heterogeneous cell populations of tumors (44) may harbor cells having both plastic and rigid networks at the same time. Moreover, as described in the previous section, cancer stem cells have the ability to change their networks from a plastic to a rigid stage and vice versa (4,6,55-57). Cancer stem cells follow Nietzsche's proverbial saying "what does not kill me makes me stronger". Thus, conventional anti-cancer therapies may actually provoke cancer stem cell development (56,65-68). In such scenarios

multi-target, combinatorial or sequential therapies using both "central hit"- and "network influence-type drugs" may provide a promising therapeutic modality.

As an important closing remark, the above suggestions have been formulated as a consequence of a large number of individual experimental studies listed in references 1 through 6. However, their applicability in anti-cancer therapies proper has only rather limited direct evidence. It will be an exciting task of future studies to show what are the applicability and limits of the above considerations in cancer pharmacology.

Conclusions and perspectives: towards a personalized drug design

This chapter listed two key network-based adaptation mechanisms. Both of these mechanisms modulate the evolvability of cancer cells to help their survival in an unpredictable environment. The first network-based adaptation mechanism was the "core-periphery learning theory" (2). Here 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. 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 to the core of their networks. The second network-based adaptation mechanism was the alteration of plastic and rigid network states (3). Alternating changes of network plasticity and rigidity help to encode novel information to the network structure remodeling the network core and developing novel system attractors. Cancer stem cells utilize this mechanism to develop an exceptionally large evolvability (4,6).

Importantly, plastic and rigid networks (mainly characterizing early- and late-stage tumors; 4,6) 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 (5-8).

Though the above suggestions have been formulated as a consequence of a large number of individual experimental studies listed in references 1 through 6, they require further experimental studies to establish their precise limits. A few of these important future research areas:

1. Further studies are needed to characterize the core-periphery mechanisms and plastic/rigid alterations of progressing cancer cell and cancer stem cell networks.
2. Systematic studies are needed to show differences in efficient targeting of various network positions in early- and late-stage tumors.
3. More system-wide studies are needed to clarify network targeting consequences of multi-target, combinatorial or sequential therapies.
4. All the above areas require extension to inter-cellular network interactions, where only a few studies have been performed yet (as a few examples, see references 69-75).
5. Both intra- and intercellular networks may be 'personalized' meaning the inclusion of the functional (e.g. signaling) consequences of the mutation profile of the given tumor and modification of network nodes and edges according to the transcriptome and proteome of the given tumor. Importantly, due to the heterogeneity of tumors, and due to 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 (at least implicitly) involved structural changes of cellular networks and have not detailed the dynamic analysis of

cellular networks determining, predicting and modifying the changes in their attractor structure. There are several important studies (such as those listed in references 42,68,76-83), which established the novel area of 'cancer attractor re-design', which develops multi-target drugs and drug combinations, which A.) do not allow the dominance of proliferation, invasiveness, etc. attractors of cancer cells; B.) act as "differentiation therapies" (48,81) guiding cancer cells back to their healthy attractors and C.) may lock cancer stem cells in their plastic or rigid phenotype.

The author is very much hoping that a paradigm-change is about to emerge in anti-cancer-therapies, where the primary target will be cancer-cell "re-education" and guidance instead of their mass-murder, and this will be performed using the emerging knowledge on network adaptation mechanisms.

Acknowledgments

The author acknowledges the contribution of current and former LINK-Group (http://linkgroup.hu) members for the conceptualization of the ideas presented. The author is a founder and advisor of the Turbine startup (http://turbine.ai) applying the attractor structure of personalized signaling networks to predict optimal intervention points of anti-cancer combination therapies. Work in the author's laboratory is supported by the Hungarian National Research Development and Innovation Office (OTKA K115378) and by the Higher Education Institutional Excellence Program of the Ministry of Human Capacities in Hungary, within the framework of molecular biology thematic programs of the Semmelweis University (Budapest, Hungary).

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