

Tumor Systems Need to be Rendered Usable for a New Action-Theoretical Abstraction: The Starting Point for Novel Therapeutic Options

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Abstract: Background: A tumor system not only consists of diverse cell types but also comprises all components of action insofar that these components are oriented in terms of diverse cell types. **Methods:** Thus, it is necessary to decode paradox situations of cellular rationalization, deformation, and communication processes or, in other words, to uncover inconsistencies within tumor cell compartments or distinct topologies of aggregated action effects. Here, a theory may be helpful that discharges into an action-theoretical abstraction and simultaneously includes evolutionary tumor developments. In an evolutionary process, tumor cells may exploit the whole extent of the rationalization features of stroma cells to implement the functional diversity of systems behavior aimed at maintaining homeostasis, and robustness in tumor systems. The introduction of genomic/non-genomic systems-directed therapeutic approaches may allow both, the uncovering of systems topologies of aggregated action effects and the broadening of therapeutic options via systems-directed approaches. **Results:** (1) Tumor systems biology is now turning into a **scientific co-subject**. (2) Developing **action-theoretical systems terms** with the corresponding conceptual equipment may contribute to the classification of tumor subsystems. (3) Systems-directed therapies may **meet new therapeutic requirements**, which might help to create therapeutic approaches that are specifically designed for the demand of tumor stages, corresponding systems stages. **Conclusions:** Therefore, patients would probably not have to be selected according to age and/or co-morbidities because of known adverse toxicities of standard therapies (maximal tolerable doses). In contrast, therapies may meet the (individual) tumor system's characteristics by a systems-orientated selection of biomodulatory acting agents. As shown, toxicities may be modest.

Key Words: Tumor systems biology, systems assessment tools.

EXPLORATIVE CONSIDERATIONS (THE 'NOW')

Cancer represents the largest genetic experiment ever conducted: Distinct acquired genetic lesions are not distributed at random in tumor cells, **despite the high variability of cancer causes**, the **heterogeneity** of observed genetic aberrations, and the **divergence** of morphologic characteristics of diverse tumor types. The non-random distribution of genetic aberrations might be explained by the fact that cancer-associated dysregulated transcription factors must still collude in a life-maintaining manner for cancer (stem) cell self-renewal, for proliferation, and for the build up of a cellular infrastructure suitable for tumor promotion [1]. As a main characteristic, cancer (stem) cells must be able to contribute to an evolutionary process. In subsystems, such as angiogenesis, inflammation must be activated and coordinated to allow expansive tumor growth. Stroma cells in the immediate vicinity are ultimately challenged, either functionally within their 'living world' (differentiation, trans-differentiation, dedifferentiation, apoptosis) or by the newly developing systems context characterized by the rationalization or the deformation of cellular functions and the acquisition of new cell types [2]. Vice versa, the function as a tumor (stem) cell is cooperatively determined by the adjacent mi-

croenvironment [3]. Many cellular functions associated with invasion and metastasis are often not constitutively expressed by carcinoma cells, but rather transiently in response to contextual signals that tumor cells receive from their stromal microenvironment [4]. Therefore, the simultaneous modeling of both stroma and tumor cell functions may open up new therapeutic perspectives in cancer therapy [5].

The communicatively designed tumor microenvironment is integrated into an evolutionary process. Thereby, it acquires cells from blood circulation and subjects cells to rationalization processes to establish new systems behavior: The higher the involvement of evolutionary processes, the higher the accessibility of 'socialization' processes of tumor and stroma cells by systems-theoretical analyses. This 'socialization' may neither be intuitively nor exclusively realized by the reconstruction from the tumor cell site, as it is commonly the case [6]. Necessary changes of the point of view and method should be conducted accurately without the confusion of paradigms. The increasingly higher organization of a tumor cell system during tumor growth results in the development of systems perspectives, in which the functional 'world' of distinct cell types is featured as a component of the respective systems 'world' [7]. Systems organizations are gaining a kind of autonomy by neutralizing separation towards previous cellular functions or by the assignment of new functions. Thus, distinct cell types obtain **systems-immanent functions** and become indifferent to other 'socialization' processes. This development characterizes the mediator-associated separation of developing tumor-adjacent

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stroma cells from a formally organized functional status within the previous functional 'world'. Conversely, experimental data support the assumption that stroma cells even impose pressure on tumor cells to change or keep functions. Ultimately, stroma cells with molecular aberrations may contribute to malignant conversion [8].

The change in systems complexity induced by a developing tumor interferes with the affected organ and may destroy not-regenerative cell inventories. Thus, this change not only alters previous ways of interactions among organ-associated cells but also considerably affects the communicative infrastructure of rationalized forms of communication within an affected organ.

It is necessary to simultaneously decode paradox situations of cellular rationalization, deformation, and communication processes, i.e. to uncover inconsistencies within tumor cell compartments by means of a theory that includes the evolutionary development of a tumor as well as its biologic history in order to increase therapeutic options with systems-directed approaches.

METHODOLOGICAL APPROACH

Theory of Communicative Interactions in Tumor Compartments

Three competing research approaches are applied regularly. As required by methodology, these approaches have to virtually dissect the coherence of systems and the functional 'world' of distinct cell systems.

Structural Differentiation

Classic methodology is comparatively classifying. The theoretical core is formed by assumptions about the structural differentiation of cells (histopathology) in functionally specialized systems of interaction. These assumptions are sufficient for supporting the observation that the structural integrity of tumor compartments needs to be maintained to sustain appropriate tumor-stroma-cell communication for tumor progression [9]. Thereby, functional considerations are not sufficiently separated from structural ones in such a way that the disposed concurrence between methodological strategies may unfold.

The likely importance of this conceptual separation was shown by Karnoub: Mesenchymal stem cells must pass through an 'educational' process to act as cells promoting metastatic process [10,11]. Investigations into evolutionary processes of tumor development discharge this theory of structural differentiation into a more theoretically oriented model that includes systems functions [9].

Considering the functional aspects of morphologic changes, Dvorak [12] developed the basic principles of this action-theoretical concept by comparatively characterizing similarities between wound healing processes and tumor growth, thereby including morphological data (structural differentiation). Although morphologically based, the introduction of an evolutionary view has allowed a systems-therapeutic approach that recalls the famous remark of Dobzhansky [13]: 'Nothing in biology makes sense except in the light of evolution'.

Tumor-associated changes in cellular structures are currently reconstructed in all intersections: More recently, much attention has been drawn to cellular stroma components that are suspected of promoting cancer progression, such as the composition of lymphocytic tumor infiltrates, fibroblasts, macrophages, and other inflammatory cells, immunosuppressive cells called myeloid-derived suppressor cells (MDSCs), and mesenchymal stem cells. Analytically attained data about these cell types allow a one-dimensional conception of the total process of structural differentiation: A distinct function is unidirectionally coupled to cellular structure.

Thus, the process of structural differentiation may not be designed as a multidimensional process, i.e. a decoupling of systems and a functional 'world' of tumor cell systems. Mediated by newly structured mediator-guided subsystems, the decoupling process during tumor development may have a decisive influence on the (still) structured differentiated functional 'worlds' of cell systems in an affected organ.

From different methodological viewpoints, the total extensiveness of tumor pathology may be highlighted only now and in such a way that would be desirable for the development of one (individual) tumor therapy with a broadened basis. However, the conceptual equipment is neither available for action-theoretical abstractions and systems-associated tumor stages nor for functional classifications based on an adequate differentiation between

- (1) synchronous structural differentiations of the functional 'world' of tumor-associated cell systems,
- (2) the spin-off of functional systems that are differentiated via chemokines and cytokines as well as the interior differentiation of these cell systems (e.g. accumulation of regulatory T-cells, mesenchymal stem cells), and
- (3) the differentiation processes induced by tumor (stem) cells, which simultaneously dedifferentiate differentiated cellular functional areas (rationalization of functions) in terms of a colonization of the functional 'world' of organ tissues (metastatic process), simultaneously facilitating the integration of new cellular elements from the peripheral blood (**mobilization, trafficking**).

Rationalization

A further competitive research approach exclusively investigates the rationalization of functional systems in the course of evolutionary growth complexity during tumor development and tumor spread under the aspect of different **purposes**. The aspect of rationalization may be elucidated by the analytically defined functional spectrum (references) of fibroblasts [14] or macrophages within a cellular system: Macrophages and other inflammatory factors do more than just foment angiogenesis in tumors [15], i.e. they actively aid cell movements that produce metastases, thereby calling tumor cells to the vessels. On the other hand, they may act as tumor-antigen presenting cells for tumor control [16,17]. This outlined functional 'world' of macrophages gives an impression of rather divergent options of rationalizations within a systems context [18]. Therefore, ambitious efforts are currently under way to retrain tumor-associated macro-

phages from immuno-suppressive tumor promoting cells to weapons that destruct tumors [19].

Stroma cells are either present in affected organs or develop after the trafficking of bone marrow-derived mobilized cells out of circulation [20]. The implementation of a new form of integration (rationalization) of these stroma cells allows an evolutionary advancement of the systems complexity with the remodeled rationalization of cellular functions: The diversified resources of tumor growth-promoting cytokines are distributed among rather different stroma-associated cell types (redundancy). Thus, different rationalization processes are conceivable without the systems deprivation of an essential growth-promoting mediator if a cell system would functionally drop out due to new systems-related differentiation processes [21]. The clue of this finding is that distinct systems functions, such as inflammation, may be maintained despite the change in cellular composition during tumor development. Furthermore, these observations underline the necessity of an action-theoretical abstraction.

Deformation

A third research approach, originally advanced by Loewenstein [22], focused on the evolutionary process of tumors with regard to the functional aspects of increasing complexity. More recent observations have followed a similar line, i.e. growth factors make cancer cell cancerous, and otherwise, if carcinoma cells are deprived of signals from the stroma compartment, they may revert to an earlier phenotype state, in which they do no longer display the traits of high-grade malignancies [23]. The question remains, how do they communicate?

With an exclusively functional consideration, the systems-associated constrictions of cellular functions, which take place in cell systems during evolution, are misplaced from the perspective of an observer on the level of communication by tethering inter-systemic exchanges at imbalances in communication. Thereby, the importance of the identity-threatening deformation of cell systems is withdrawn, as it is appreciated from a participator's perspective: Tumor-associated stroma cells may even be driven into apoptosis by systems characteristics: In a figurative sense, they are neutralized by the system [24].

Resulting Observation Levels

Pathologic systems-biological processes in cancer may be reported from different observation levels:

- (1) in Loewenstein's view, pathologic cancer processes are predominantly mirrored in deficient cell-to-cell communication [22],
- (2) the initial source of observation may also be an altered systems-associated cell composition [25], and
- (3) distorted functions of single cell systems within the tumor microenvironment [24-27]: Deformations.

In tumor systems biology, diverse 'wound healing' processes, such as inflammation and angiogenetic processes, have been identified as factors independent of the viewpoint of observation.

Approach to an Action-Theoretical Systems Term: The Scientist as a Subject of the System

Each of the three research approaches and viewpoints described bring about the **separation of subject and object**. In other words, none of the three approaches considers it necessary to uncover the object: **A tumor's systems biology is also a scientific subject**, a co-subject of the scientist that interests not only as an approach for observation, description, and explanation of cellular behavior. Even more, it serves as a communication partner, for instance via biomodulatory therapies, and thus as an approach of hermeneutic comprehension. This approach represents a scientifically new aspect for understanding tumor biology, implicating a decisive broadening of therapy options that arise from the evolutionary consideration of tumor development [5].

Tumor Systems Need to be Rendered Useable for a New Action-Theoretical Abstraction

The constitution of this new kind of consideration about the **objects of interest** an action-theoretically derived (therapy-related) systems theory is different from the exclusively analytic/empiric systems terms that derive from results generated by functional genomics/proteomics in tumor systems biology.

Assignment of Systems-Theoretical and Action-Theoretical Inconsistencies

The systems concept in tumor biology is introduced by a systematic recording of the functional 'world' of single cell types including their potential contribution to communication. The change from the perspective of an observer to that of a participator is justified by the action-theoretical description of a system in biomodulatory therapies [5]. Thus, a new frame for action may be launched for new systems-directed therapies, which may affect tumor growth by regulatory activities and thereby modulate functions of subsystems that could be found ubiquitously or in distinct tumor groups and different tumor stages. This concept has been outlined especially for metastatic stages [5].

CONCEPTUAL EQUIPMENT

Behavior dispositions, behavior reactions, behavior-releasing stimuli. In a cell system, we have to differentiate between the reactions of a cell system on mediators, the addressing of reactions to other cell systems, and the addressing of another cell system calling out the response. A system of fundamental terms (behavior dispositions, behavior reactions, behavior-releasing stimuli) permits the separation of cellular behavior from observable events. Thus, tumor systems may be rendered useable for a new functional systems classification, the starting point for new therapeutic options. Behavior dispositions may have a great impact on tumor growth. This assumption is underlined by the claim that attempts at determining metastatic tumor properties should focus on genes and proteins that confer the responsiveness of a primary tumor cell to stroma cells, rather than on genes and proteins that directly mediate the cellular phenotypes of invasive metastasis [10].

Systems-directed tumor therapy: Uncovering and meeting diversity of tumor systems

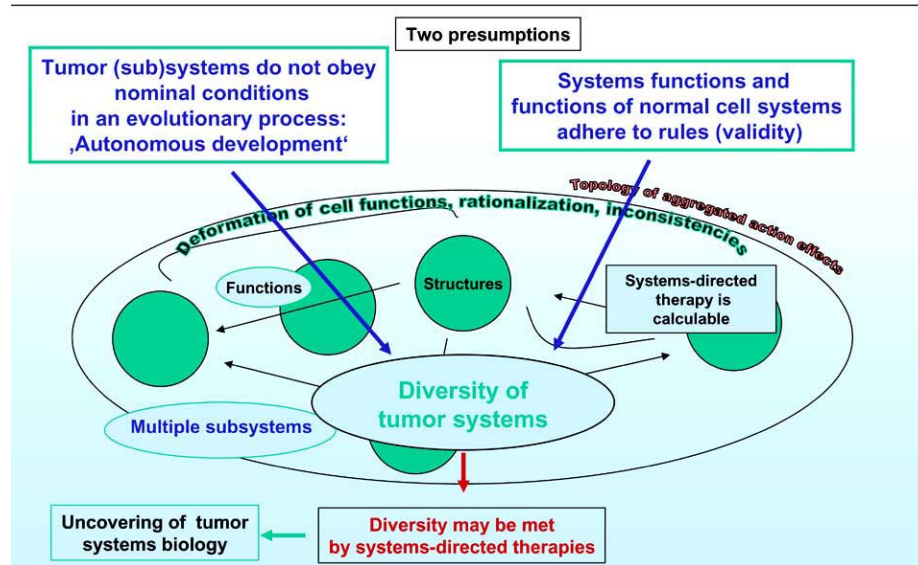


Fig. (1). Systems-directed therapies may integrate action-theoretical systems terms (theory) and biomodulatory therapy-derived comprehension (experimental part) of tumor-associated subsystems (e.g. inflammation, angiogenesis...), thereby uncovering and meeting diversity of tumor systems.

Denotation and identity of a cell or a cell system. Inter-cellular relations within the tumor compartment are reconstructed from the perspective of distinct cell systems, which represents the most frequently used reconstruction. Here, the notion of rules comes into play. The application of a rule induces the assignment of symbols (e.g. pathway structures) and the assignment of an identical denotation and validity.

For the introduction of functional aspects into tumor pathology, it is important to note that the denotation of cell systems does not necessarily derive from the identity of the object, for instance morphology, which may be identified as an identical cell system by a different observer.

Macrophages, fibroblasts in tumor stroma, and their multifaceted functional stages represent an exceptional example: Their identity comprises diverse realizations of functions within different systems conditions, which means that identity is not based on observable invariance but on **intercellular validity**. Vice versa, the identity and validity of rules are related between cell systems (Fig. 1).

Role structure between cell systems. Obviously, standardized anticipation of distinct behavior seems to exist, considering the constitution of a growth-promoting microenvironment based on distinct tumor (stem) cell functions. Nevertheless, new communication pathways may be initiated that are related to the new functional 'world' of tumor cells. However, cell system A does not know, whether it adheres to a rule, or if is exposed to the susceptibility of cell system B or to the ability to reach consensus (educational processes). Educational effects have been observed in tumor systems [10].

Autonomy. A typical feature of the establishment of tumor systems is that their formation empirically depends on

the specific prerequisites of a host's organism. Also from an empirical viewpoint, subsystems may develop a certain autonomy (for example, inflammation and cancer-associated autoimmunity). Although tumor systems may not exist beyond a social cellular system, just the same as subsystems without a tumor system, these subsystems may vary independently to some extent and could contribute to border-line histology (Fig. 1). Additionally, cell systems may not constitutively generate functions, which may also be transiently acquired by 'education' for a small time frame [10].

Subsystems may be independent to a certain degree, i.e. they do not feature characteristics as invariable references, must steadily advance **contingent relations** to one another, and are not fixed to invariant features of developmental stages. Contingency programming may adapt interactions via adhesive interactions with stroma cells, stroma proteins, and growth factors [28]. However, relations of subsystems are predetermined by their affiliation to a common action system. Subsystems are forming environments for one another, but in a regulated trade-off.

Reproduction. Each action system presents itself as an area of reciprocal interpenetration of subsystems. Each of these subsystems is specialized in reproducing basic functions facilitating tumor promotion. The distinct reproductive function of tumor (stem) cells is underlined by molecular-pathologic data showing that molecular aberrations in the primaries determine tumor biologic behavior, for instance, early or late metastatic spread as well as metastatic sites [29,30].

Evolutionary processes. Basically, tumor development is comparable with an evolutionary process, during which single cell systems acquire to a greater or lesser extent (area of application within the communicative exchange) diversified

Evolutionary process of tumor development: Terminology

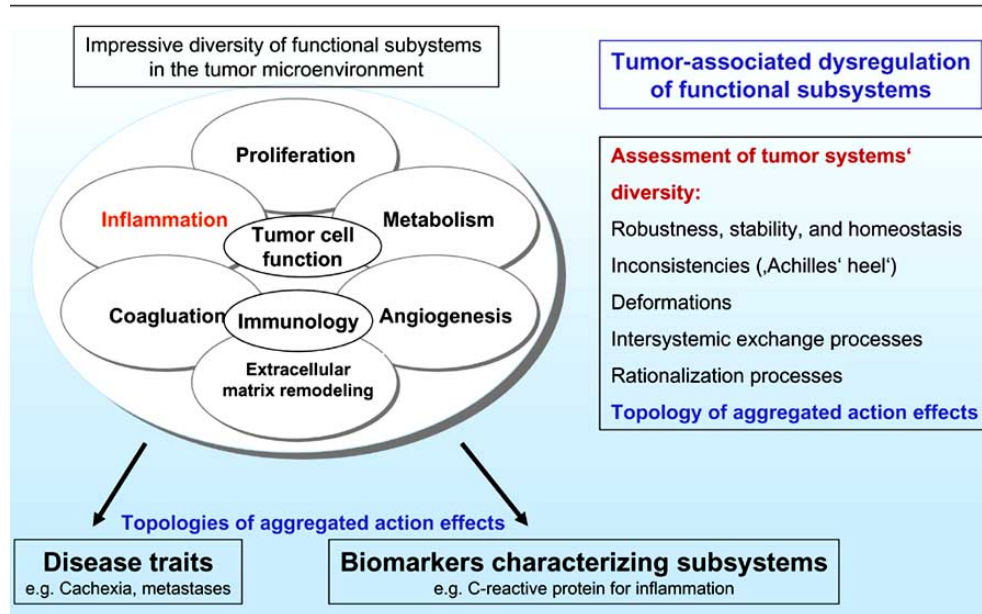


Fig. (2). Assessment tools of systems biology are rationalization processes, inconsistencies, deformations, altered inter-systemic communication, and topology of aggregated action effects. The more exact systems biology may account for the objects of interest studied by means of these tools, the more it may justify the use of systems-biological research approaches.

cellular functions due to changing and increasing systems complexity (for example, integration of extensive inflammation during metastatic spread). Cell systems experience pathologic deformations in case of inconsistencies between the functional 'world' and the systems 'world' and may even be driven to apoptosis. Now, in the mirror of evolutionary processes, the functional 'world' of cell systems may be recognized under systems-therapeutic conditions and vice versa [5,31] (Fig. 1).

Sensitive Assessment Tools (Fig. 2)

Clinical phenomenology, hermeneutic observation of systemic exchange of information during evolution, and systems-targeted therapies represent action-orientated research approaches. How may systems pathologies be conceptually characterized?

Robustness, stability, and homeostasis of a tumor system describe how a subsystem is controlled during biomodulatory therapies or evolutionary processes [32]. By means of biomodulatory therapies, the following observations within phase II trials on different metastatic tumor types indicate therapy-related alterations of tumor **robustness, stability, and homeostasis** in a therapeutically relevant way:

- (1) stable shaping of and focusing on the tumor system's organization (very delayed objective),
- (2) significant modulation of tumor-associated disease traits, for instance, inflammation, ECOG status, paraneoplastic syndromes (biomodulation-derived biomarkers),

- (3) biomodulatory activity depending on the metastatic organ site in HRPC (tumor-stroma-specificity as expected from the known differential behavior of various cell types within tumor compartments and varying stroma cell compositions at different metastatic sites), and
- (4) the predominant site of progression at the original localization of metastases (hints for impact on metastatic processes) [5].

Changes of systems characteristics, cumulative activities (positron emission tomography, PET), and biomarkers (e.g. C-reactive protein) were recorded by monitoring functions and components of subsystems (for instance, inflammation, angiogenesis, etc.).

Inconsistencies: Pathologies arising from 'social' interactions of cell systems may not be matched with **nominal conditions**. This circumstance has to be met from a systems-therapeutic view: Systems-immanent pathologies may emerge as **inconsistencies**, in which communicative networked interactions between cell systems may be involved. 'Fallacies', 'self-delusions', or 'instigations' may objectively apply force to organisms [8,20-24,33]. Misleading communicative contributions are provoked by an interactive communication praxis (for instance, tumor-associated autoimmune phenomena), which depends on the areas of application (conspirative behavior of a body's own normal cells), thereby limiting the operational praxis and response repertoire of cell systems. 'Fallacies' may occur as communicative processes that are to limited extent critically appreciated by neighboring cells. Markert phrased the presumption that

'very little cell differentiation is truly autonomous in vertebrate organisms' [31]. However, tumor cells may exploit the whole extent of stroma cell autonomy to implement the functional diversity of systems behavior, which is mirrored in highly diversified rationalization, deformation, and communication processes aimed at maintaining homeostasis, stability, and robustness of tumor systems. These systems characteristics may be mapped in distinct topologies of tumor systems-aggregated action effects. A way to uncover these aggregated action effects are biomodulatory therapy approaches [5].

'Fallacies' are likely to play an important role in cancerogenesis and progression as well as in the development of benign tumors. Vice versa, inconsistencies offer an operational range for systems-directed therapeutic approaches [5,17,19,23,34,35].

Furthermore, the interference of inconsistencies could also explain the durable and sometimes rapid therapeutic responses observed in highly vascularized tumors such as angiosarcomas and renal clear cell carcinomas. These responses also occur in pronounced inflammatory tumors, for example, in Langerhans' cell histiocytosis. Inconsistencies targeted with genomic/non-genomic biomodulatory therapy approaches could bring about a collapse of overstressed hyperactive communication systems that maintain distinct functional stages [5]. Also self-depictions arising as tumor-associated autoimmune phenomena may be controlled by biomodulatory therapy approaches [36]. An impressive example for self-depiction during tumor initiation seems to be the autoantigen-triggered evolution of chronic lymphocytic leukemia (CLL) [33].

Deformations: Abstractions of inconsistencies in which networked cell systems may be involved, thereby discharging in paradox pathologies, may arise as deformations of cell systems including their functional spectrum. Other paradox processes may be uncovered by analyzing rationalization processes. Paradox processes can be of such quality that a systematic congestion caused by rationalization of the functional 'world' of tumor-associated stroma cells may result in an overload of communicative infrastructures (for instance, Langerhans' cell histiocytosis). Paradox processes may be monitored by analyzing the diversification of rationalization or deformation processes, or, in extreme cases, apoptotic cell death [24].

Functional pathologies become evident because of the interactive communication praxis of cell systems assigned to areas of application: spontaneous tumor necrosis may also be understood as functional pathology. Here, the tumor microenvironment may not maintain or advance the originally constituted system in an evolutionary context. Additionally, no controlled degradation takes place after damage of systems functions.

In case of tumor (stem) cells, the identity of the denotation and the object itself is never the same (quiescent, tumor-promoting phase). Therefore, 'deformation' of a tumor (stem) cell may also result from a neutralization process (in contrast to active controlling, for example, immunologically). As the importance of a tumor cell in the role of a tumor-promoting cell is critically influenced by the tumor-

associated microenvironment, targeting of tumor (stem) cells via microenvironment seems to be therapeutically promising [3,5,37]. The fact that a cancer (stem) cell must be promoted by a number of inflammatory conditions, particularly in the metastatic stage of cancer disease, fits with the successful use of anti-inflammatory therapy components in the systems-targeted treatment strategy presented recently [5].

Metastatic spread may be promoted by a series of rather different cell systems invading the tumor compartment. Despite the presence of cancer cell dissemination in different organ sites, release from dormancy and growth are selective for particular organ sites and depend on stroma composition but not on one singular cancer cell-driven process [29,30].

Intersystemic exchange processes: The complimentary reciprocal activity, which subsystems may generate for one another, may be analyzed as currents of inter-systemic exchange. Therefore, from a therapeutic point of view, the systems-biological model does not specify whether a 'wound healing mechanism' has to be suppressed or stimulated to achieve tumor control: Inflammation control as well as stimulation of inflammation may control tumor growth, immuno-suppression, and immune stimulation [5,34]. Contradictory decisions could be associated with the same capacity to achieve tumor control in a distinct tumor type. Thus, the questions arising are: which therapeutic approach would be easier to put into practice, which is likely to be more compatible with other therapeutic approaches, and which is the most tolerable approach with regard to side effects.

Action-oriented Research Approaches: Broadening of the Therapeutic Spectrum (Individualized Therapy)

Topology of aggregated action effects: Detection of **inconsistencies** between the action status of a cell type and the systems organization within a tumor engross the insights into the pathophysiological organization of important functional elements and constellations discharging into a distinct topology of aggregated action effects [5]. Characteristic constellations may be ubiquitously found in rather different tumor types (for example, highly 'pro-angiogenic' 'inflammatory' tumors) and, therefore, beyond a specific tumor type or its distinct organization of subsystems (Fig. 3). Consecutively, a broad repertoire of biomodulatory therapy approaches targeting the **functional status** of cell systems **or cell communication** should be available for targeting functional pathology (individual) constellations at low toxicity levels. Concerted modulation of transcriptional networks via peroxisome proliferator-activated receptor (PPAR) alpha/gamma agonists, interferon-alpha, glucocorticoids, PPAR-delta antagonists, metronomic low dose, angiostatic and immunomodulatory acting chemotherapy have shown a wide activity in metastatic tumor control, even the capability for remission induction [5,38-41]. The cellular microenvironment may even modulate via orphan receptors a set of transcription factors characterizing 'stemness' of tumor cells, e.g. Okt 3/4 genes [42-45]. Do systems complexity and the myriad of reductionist therapeutic approaches targeting tumor or stroma cells precede the simplicity of biomodulatory treatment strategies?

The repertoire of drugs abruptly expands with the introduction of systems-therapeutic concepts, as (1) substances with unintended indication, such as drugs modulating the

The new object of interest: Uncovering tumor systems biology

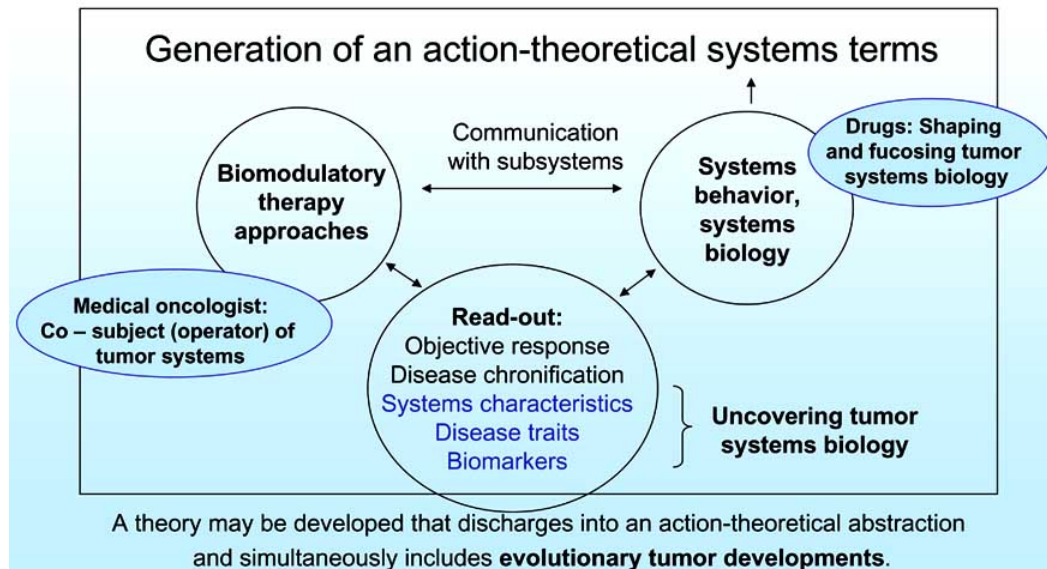


Fig. (3). Practical and emancipatory interests in therapies integrated in the coherence of science bring together the constitution of new objects of interest (therapy-derived systems biology) and their pragmatic application, here in form of biomodulatory therapy approaches. Biomodulatory derived changes in the tumor may demerge individually moving processes within the tumor tissue into more easily elusive constellations.

transcriptional networking, may be introduced [46,47]. (2) Contrary to the molecular genetic heterogeneity of tumor cells, tumor growth-promoting systems promise a high grade of similarities (for example, angiogenesis and inflammation). Therefore, a similar repertoire of drugs might be available, which target and regulate corresponding tumor-associated subsystems mirrored by biomarkers [48]. (3) Targeting functionally defined subsystems seems to become of increasing interest, as subsystems may be exclusively functionally defined in a systems context but simultaneously linked to alternating structural systems [21]. Targeting functional systems structures opens up a new therapeutic window favoring concerted biomodulatory strategies. (4) Beyond that, it should be possible to abstract traditionally described subsystems: Drugs with biomodulatory activity as (nuclear) transcription factors regularly have an activity profile far above the capacity of hermeneutic comprehension [5]. Transcriptional networking may have a decisive regulatory impact on tumor promotion, for instance, on the angiogenic switch or on tumor stem cell behavior [37]. Indeed, the abdication of hermeneutic comprehension was a prerequisite of modern science. To what extent is comprehension necessary for describing tumor biology from an action-theoretical view (Fig. 4)?

1. From a different point of view, subsystems are also action and functional systems (genome, transcriptome, proteome [pathways], cellular, extra-cellular microenvironment, tumor [stem] cell, tumor-associated disease traits). By no means do they accentuate only arbitrary systems. The classification

of subsystems has not only a theoretical but also a practical impact, as the benchmarks of the systems correspond to the components of which functional sequences are composed.

2. Systems-biological approaches are open for the detection of new networking interactions (experimental part). Thereby, the context of discovery (modulation of tumor-associated disease traits, biomarkers) has to be consistently separated from the context of justification (rational for a biomodulatory therapy approach).
3. Basically, a hermeneutic comprehension of action mechanisms within familiar observation levels is no prerequisite in respect of the multi-fold co-regulative and the cell-specific activities of (nuclear) transcription modulators in different cell systems. In contrast, the currently established genomic/non-genomic biomodulatory therapies may lead to novel and more abstract perspectives for viewing the topology of tumor systems biology [5].

Discussion: Critical reflection on tumor systems biology (the ,then')

The uncovering of tumor systems requires more than analytical approaches, for instance, the use of research approaches, such as phenomenology (including case reports, description of therapy-associated side effects), hermeneutic understanding, theory of evolutionary processes, and systems-directed therapies.

Modulation of disease traits: To what extent is comprehension necessary for describing tumor systems biology from an action-theoretical view?

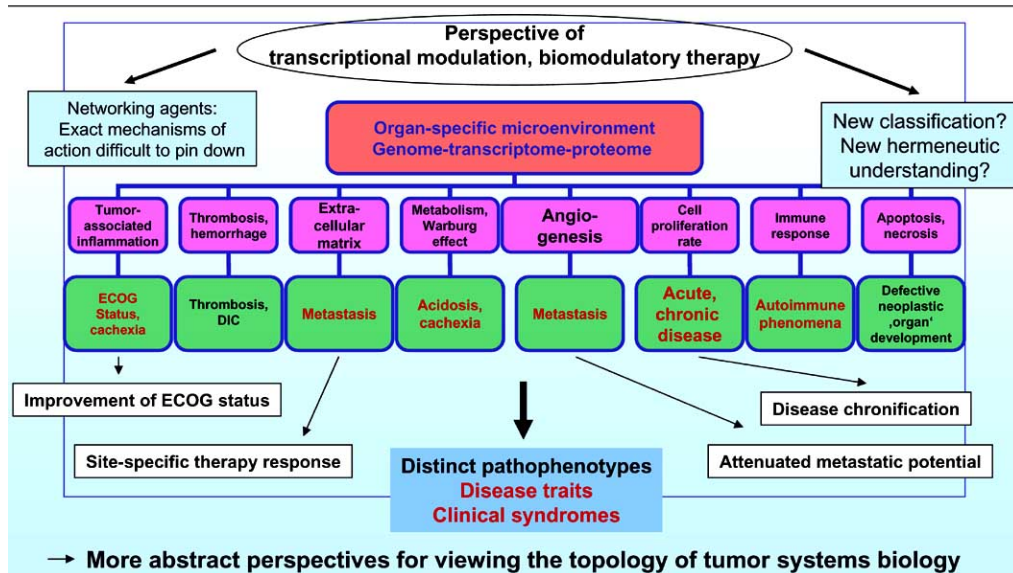


Fig. (4). Systems-biological approaches are open for the detection of new networking interactions (experimental part). Thereby, the context of discovery (modulation of tumor-associated disease traits, biomarkers) has to be consistently separated from the context of justification (rational for a biomodulatory therapy approach). The currently established genomic/non-genomic biomodulatory therapies may lead to novel and more abstract perspectives for viewing the topology of tumor systems biology.

Assessment tools of systems biology are rationalization processes, inconsistencies, deformations, altered inter-systemic communication, and topology of aggregated action effects. These tools are only now emerging in their constellation during tumor development (in different tumor types and stages) as a decoupling of systems and the functional ‘world’ of cell systems. The more exact systems biology may account for the objects of interest studied (for instance, the topology of aggregated action effects) by means of these tools, the more it may justify the use of systems-biological research approaches (Fig. 5).

Currently, the instruments for merging different scientific directions for systems-theoretical considerations are missing. Basic research is predominantly technology-oriented, aligning itself with the dichotomy of structure- and function-analytical problems. Closer collaboration between academic institutions and biotech and pharmaceutical industries will be required to facilitate research on systems-biological processes [49].

A tumor system as a system of action consists not only of diverse cell types but comprises all components of action insofar that these components are oriented in terms of diverse cell types, the system’s objects. Cumulative knowledge, though scientifically acquired, is more specifically a complex of meanings symbolized within distinct references to different cell types: References are dissipating from the view of a participator (systems biology as a co-subject of the scientist) and cellular functions are anticipated as rationalization processes. The diversity of rationalization processes is

based on the intercellular validity of communication rules and might be generally an explanation for the large amount of cases in which cell cultures or animal models cannot be transferred into clinical praxis.

An action-theoretically oriented tumor model diversifies therapeutic instruments by uncovering new systems qualities that may be targeted by broadening therapeutic options by the introduction of biomodulatory approaches. Now, therapies may be guided by monitoring (new) functional pathophysiological processes (biomarkers): If biomodulatory therapies remove differential cell or systems functions involved in metastatic progression, the metastatic process may be inhibited as shown in our systems-directed genomic/non-genomic therapeutic approaches [5] (Fig. 6).

Therefore, the most important task is to look for common systems features (‘topologies’, inconsistencies) within different tumor types to get action-theoretically guided classifications of distinct tumor-associated evolutionary systems processes. Furthermore, classification is essential, as classification is the basic language of medicine and systems organizations across different tumor types, which need to be clearly defined. The uncovering of common features in different tumor types is only the beginning: Lymphomas could soon be classified according to their activation of inflammatory signaling pathways [50], common stroma gene expression sets may be detected in response to tumor invasion [51], neoplasias may be classified according to their responsiveness towards combined modulation of transcriptional networking [5], and so on. Another attempt may be the formula-

Shaping and fucosing the tumor's organization: Dynamic character and therapeutic implications

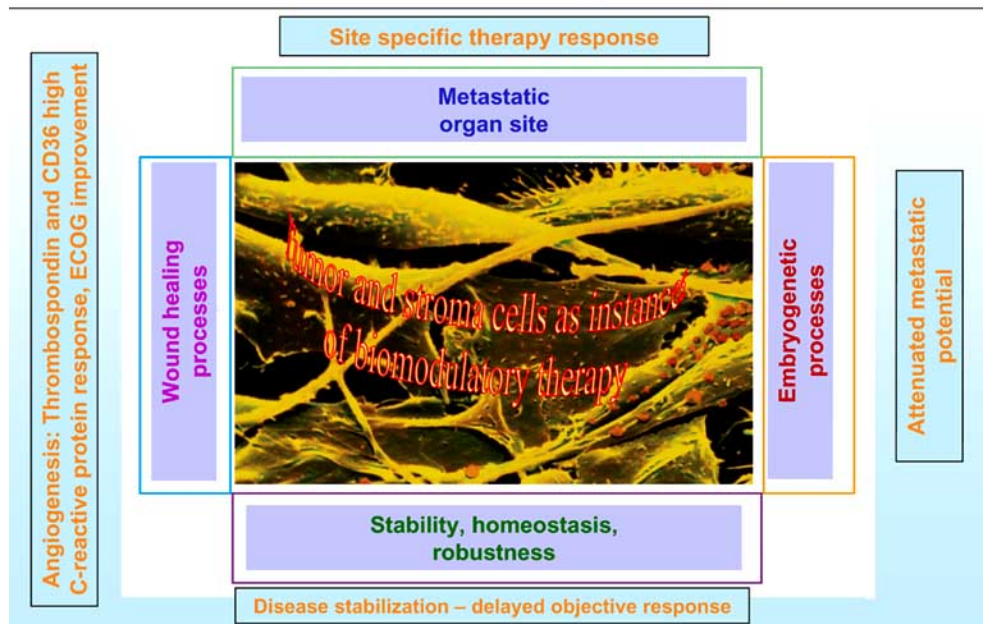


Fig. (5). Multifaceted shaping and fucosing of the tumor's organization is the result of multitargeted biomodulatory therapy approaches including stimulatory and regulatory agents with pleiotropic activity and known poor or no monoactivity within the respective tumor type: Dexamethasone, pioglitazone, interferon-alpha, COX-2 inhibitor, metronomic low-dose chemotherapy.

Systems biology: How to break through the complexity barrier? Generation of differentially induced tumor(stem)cell-stroma-organisations



Fig. (6). Cellular functions of neighbouring stroma cells are decisively influenced by the tumor cells. The stroma cell proportion within the tumor compartment is highly sensitive for biomodulatory therapy approaches due to the dynamic character and the context-dependent dichotomous activities of stroma cells.

tion of stroma scores, which still seems to neglect functional system aspects [25].

Action-theoretical systems-terms may additionally contribute to the classification of tumor subsystems via new

biomarkers: The method to uncover action-theoretical systems terms is now pioneered from bedside to bench. Clearly defined and distinctive functional systems similarities could be the basis for administering a specific repertoire of (bio-

modulatory) medications during distinct functional tumor systems stages. The functional status of different systems constellations may be monitored by respective biomarkers. This perspective allows a new comprehension of individualized therapy. Especially the time-sensitivity of a therapeutic approach may be addressed.

In the near future, biomodulatory therapy approaches of metastatic tumors could be methodological tools of an **individualized tumor therapy**: In contrast to 'causal' therapeutic approaches aiming at the blockage of aberrant tumor-associated pathways by a restricted repertoire of highly specific drugs, multiple potential modulators (activators and deactivators) of transcriptional processes are available for biomodulatory therapy approaches. According to our experience, mono-activity of a single transcription modulator is no prerequisite for its successful use and the combined administration activity of all modulators could be followed by respective biomarkers. Close monitoring would further allow us to choose other modulator combinations in cases of weak interactivity to facilitate an objective tumor response [5].

The introduction of sophisticated technologies, such as microarray analyses, pathway analysis in cancer and stroma cells, and accompanying translational research, has caused some fundamental biological understanding of complex cell interactions associated with important therapeutic implications [52,53]. Analytically and empirically obtained data are important, including the myriad of prognostic markers: But the systems perspective offers the opportunity of weighing constellations as well as pathophysiologically important elements for tapping new treatment strategies!

A striking difference is visible in the **pragmatic function**, which generated data in different scientific areas. Here, we can combine therapeutically derived information on systems biology to establish systems-biological models. Information may be generated on three levels: Biomodulatory processes, tumor response (traditionally tumor shrinkage), and side effects on the level of the whole organism. Systems-biological considerations may pave the way via new sources of prognostically relevant biomarkers that are representative for subsystems to convey transparency of systems-analytical accessible systems topologies, which may be targeted by (biomodulatory) genomic/non-genomic systems-orientated therapies.

Systems-directed therapies could meet rather new therapeutic requirements. Studying systems biology may help to create therapeutic approaches specifically designed for the demand of tumor stages, corresponding systems stages, and involved organ sites. In this context, the clinical discussion about the appropriate clinical study endpoint is coiled up again: Chronification of metastatic disease or induction of complete remission? Some types of cancer can be held in check by means of stroma by causing cancer cells to behave more like normal cells [5,54].

An important consequence may arise from the cumulative knowledge about mostly unidirectionally analyzed cellular systems interactions on the one hand and the accumulation of results of action-theoretically defined systems terms on the other hand: Patients would probably not have to be selected according to age or comorbidities or both because of

known adverse toxicities of empirically evaluated 'standard' therapies (maximal tolerable doses) as in case of administering systemic and exclusively reductionist therapies. On the contrary, therapies may meet the (individual) tumor's systems characteristics by a systems-orientated selection of biomodulatory acting agents. As shown, toxicities may be modest [55]. Therefore, therapies could 'come' to the patient.

ACKNOWLEDGEMENTS

This work was greatly facilitated by the use of previously published and publicly accessible research data, also by philosophical considerations of J Habermas, K-O Apel, JR Pierce and T Parsons. I would like to thank M Schoell for the critical review of the article, and all the colleagues contributing in the multi-center trials.

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