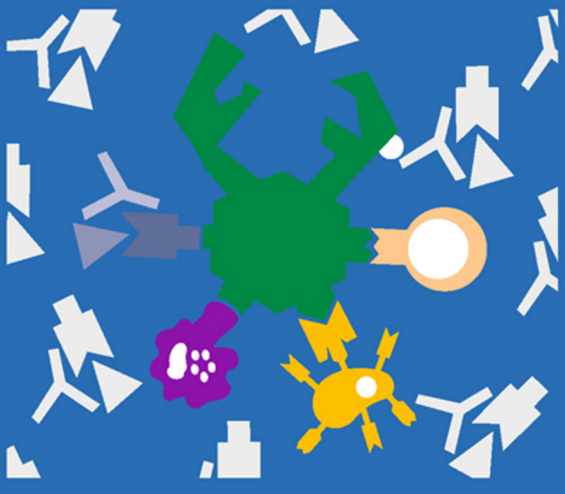
The Tumor Microenvironment 3

Series Editor: Isaac Witz

Albrecht Reichle
Editor

From Molecular to Modular Tumor Therapy

Tumors are Reconstructible Communicatively Evolving Systems



Springer

From Molecular to Modular Tumor Therapy

The Tumor Microenvironment

Series Editor: Isaac P. Witz

For other titles published in this series, go to
www.springer.com/series/7529

Albrecht Reichle
Editor

From Molecular to Modular Tumor Therapy

Tumors are Reconstructible Communicatively Evolving Systems

Springer

Editor
Albrecht Reichle
Department of Hematology and Oncology
University Hospital of Regensburg
93042, Regensburg, Germany
albrecht.reichle@klinik.uni-regensburg.de

ISBN 978-90-481-9530-5 e-ISBN 978-90-481-9531-2
DOI 10.1007/978-90-481-9531-2
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2010935488

Contents

Part I
Therapy-Derived Systems Biology: A Pragmatic Communication Theory

Chapter 1
Bridging Theory and Therapeutic Practice: From Generalized Disease Models to Particular Patients

Albrecht Reichle

Abstract The traditional problem of the poor presentability as well as diagnostic and therapeutic practicability of individual patient care is still unresolved. Biomodulatory therapies for metastatic tumors bring transparency into tumor systems by breaking into a tumor's holistic communicative world, and by dissecting the tumor for practical purposes, such as attenuation of tumor growth, in comprehensible evolutionary processes. Biomodulatory therapies show that the holistic communicative structures of a tumor are now an experimentally and therapeutically accessible entity: Communication within systems—which is self-content to some degree—works with the implicit understanding that (1) the validity and denotation of particular systems objects (proteins, cells etc.) is always context-dependent, (2) the validity and denotation of the systems objects may be therapeutically redeemed by systems-immanent communication rules, which are determined by descriptively accessible communicative systems textures including intersystemic exchange processes. The difference between theory and practice may be decisively attenuated (1) by giving reductionistically derived systems features an internal communicative context (formal-pragmatic communication theory), (2) by introducing a novel and scientifically accessible perspective, i.e. the tumor's 'living world', which is defined as a tumor's holistic communicative world, and (3) finally by binding the systems features to tumor-immanent evolutionary processes (modularity of biochemical and cellular processes, rationalization of tumor functions).

The newly discovered tumor-associated systems architectures, which are built on the capability of tumor systems to modularly rearrange the validity and denotation of systems objects, clearly differ from the reductionistically derived systems comprehension: (1) Communicatively-derived systems structures offer new insights into evolutionary processes, promoting tumor development and expansion into the 'metabolism' of tumor evolution. (2) Based on the perception of a systems participator, we ultimately leave behind typical reductionistically derived teleological

A. Reichle (✉)
Department of Hematology and Oncology, University Hospital Regensburg,
Franz-Josef-Strauss-Allee 11, 93053, Regensburg, Germany
e-mail: Albrecht.reichle@klinik.uni-regensburg.de

A. Reichle (ed.), *From Molecular to Modular Tumor Therapy*,
The Tumor Microenvironment 3, DOI 10.1007/978-90-481-9531-2_1,

systems features. (3) Both, reductionist and holistic understanding are exerted to reproduce a situational stage of tumor disease: Differential perspectives of therapeutic interaction are entangled with various levels of knowledge and consecutively with different therapy strategies.

Keywords Personalized tumor therapy • Communication theory • Metastatic tumor • Tumor models

1.1 Introduction

The traditional problem of the poor presentability as well as diagnostic and therapeutic practicability of **individual patient care** is still unresolved. Applied science subsumes particular tumor features in general patient models without attending to individual, evolutionary-developed systems patterns in metastatic tumor disease.

For a patient as an **individual**, no difference exists between the patient as a general and as a particular person. In the present context, the term 'general patient' refers to the biochemical, cellular, and organ unity or, in other words, to the empiric patient among many other patients with identical reductionistically derived characteristics. The particular patient, on the other hand, is characterized by distinct individual and even particular therapeutically accessible features (e.g. via the tumor's Achilles' heel).

When the knowledge about a patient is generalized and projected into a unique cohort – meaning that one patient is the representative of an entire patient population, – the general oncologic knowledge meets the **nude identity of the tumor patient** as a formal prerequisite of the coherency of the physicians' conceivability. If the knowledge about a disease is empirically derived, i.e. based on the view of clinicians, the internal nature of the disease is perceived as foreign as its external nature, namely that of a whole patient population with distinct biological stigmata.

If differentiation between the accepted situational notion and the 'transcendentally' true notion of an individual disease ceases, that means disease perception under idealized conditions of a 'homogeneous' patient cohort, we are unable to explain, why we can reflexively learn and improve our own knowledge and standards in patient care.

We may not accept our notions about an individual patient – which are always only locally and time-dependently justified – to be true in an objective sense.

The conflict between intelligible, classifiable model diseases and an individually emerging disease needs to be overcome by **contextualist diagnostic and therapeutic approaches**. Scientific ambition for objectivity in the comprehension of metastatic tumor diseases is marked by the search for intersubjective agreements. Scientists present data sets and applied tumor models generated either by sophisticated technologies (e.g. 'omics') and mathematically reprocessed data or by the pure availability of drugs for combinatory use (combination of 'historical' standard therapies with novel therapy principles). Subsequently, these data sets are incommensurable, resulting in divergent comprehensions of metastatic tumor diseases and finally in the call for novel 'ontologies'.

The present book aims at leading the reader away – in a scientifically accessible manner – from the daily conflicts between **theory and practice** and between **the generalized and individual tumor patient**, so that more personalized diagnostic and therapeutic strategies can be developed for controlling metastatic tumor disease:

- First, recording the systems concept of tumor biology based on rather different sciences (biochemistry, cell biology, and medical oncology) in form of the functional world of single tumor-associated cell types (tumor microenvironment and tumor cells) and respective biochemical processes (with the main focus on inflammation) including their potential contribution to communication
- Then, giving reductionistically derived systems features an internal communicative context (formal-pragmatic communication theory)
- Finally, binding the systems features to tumor-immanent evolutionary processes (modularity of biochemical and cellular processes, rationalization of tumor functions)

As shown, the difference between theory and practice may be decisively attenuated by introducing a novel and scientifically accessible perspective, i.e. **the tumor's 'living world'**, which is defined as a tumor's holistic communicative world. Addressees and receivers of communicative processes are the systems objects of a tumor, i.e. molecules, pathways, cellular organelles, cells, and the host's organs. The texture of a tumor's 'living world' consists of structured systems-wide contexts.

Communication within systems – which is self-content to some degree – works with the implicit understanding that

- The validity and denotation of particular systems objects is always context-dependent (integration of addressees, receivers of communication, including their signals) and subjected to contingency programming.
- The validity and denotation of the systems objects may be therapeutically redeemed by systems-immanent **communication rules**, which are determined by descriptively accessible **communicative systems textures** including **inter-systemic exchange processes**.

The texture of a tumor's 'living world' allows the implementation of a 'big functional world' inside small tumor networks, if modular tumor architectures are successfully rearranged by **biomodulatory tumor therapies** (modulators of transcription factors, low dose metronomic chemotherapy, Imides, histone deacetylase inhibitors, etc.) to attenuate tumor growth with **modest toxicity**.

That way, the **conflict** between context-disrupting claims for generalized diseases with their attributed reductionistically derived features and the availability of situational patient-derived tumor-associated features **may be resolved**. Therapeutically emerging tumor-associated features in form of action- and therapy-relevant yes/no statements mirror the therapeutic facts at an involved organ site. Objective tumor response or stable disease resulting from communicative interference with tumor systems is mediated by biomodulatory therapy approaches.

The holistic communicative concept of tumors described in a **formal pragmatic communication theory** does not give in to a generalized, commonly used 'homogeneous' tumor model (which hardly includes the individuality of a tumor disease, despite the general assumption of individually varying tumor evolution). Additionally, this holistic concept does neither agree with the frequently valueless subjectivity of individual diagnostic and therapeutic decisions nor with a circular concluding teleology (e.g. tumor cell selection comprehended as the competitive 'survival of the fittest' in the Darwinian sense).

At first sight, the fact seems rather daunting that all systems processes are subjected to a continuous contingency programming on the basis of tumor-immanent, partly autonomous and, therefore, individually evolving processes. However, when we therapeutically meet the challenges presented by a tumor's 'living world', we may achieve **therapy-derived systems interpretation** including individual but also classifiable processes linked to distinct **situational, stage- and tumor type-associated evolutionary developments**.

The newly discovered tumor-associated systems architectures, which are built on the capability of tumor systems to modularly rearrange the validity and denotation of systems objects, clearly differ from the reductionistically derived systems comprehension:

- The holistic communicative structures of a tumor are now an experimentally and therapeutically accessible entity.
- Communicatively-derived systems structures offer new but not teleologically preconceived insights into evolutionary processes, promoting tumor development and expansion into the '**metabolism'** of **tumor evolution**.
- The holistic communicative view allows a more abstract systems perspective of tumors.
- Based on the perception of a systems participator, we ultimately leave behind typical reductionistically derived teleological systems features (i.e. tumor-associated angiogenesis, immunology, inflammation, coagulation etc.).
- Both, reductionist and holistic understanding are exerted to reproduce a situational stage of tumor disease: **Differential perspectives of interaction** are entangled with **various levels of knowledge** and consecutively with **different therapy strategies**.

Tumor-associated evolutionary processes exclusively lie in a communicatively-linked molecular and cellular world. Biomodulatory tumor therapies bring transparency into the holistic communicative system by breaking into a tumor's 'living world' and by dissecting the tumor for practical purposes, such as attenuation of tumor growth, in **comprehensible evolutionary processes**.

Knowledge about these processes may finally **bridge theory and practice** in a novel appreciation of **tumor pathophysiology** and in novel biomodulatory-based **study designs** (adaptive trial designs). Systems-related read-out parameters derived from cellular **secretome analytics, molecular imaging techniques**, **and comparative systems analytics of different tumor types and systems stages** are urgently needed to describe modular, evolutionary developing tumor architectures and intersystemic exchange processes.

At the end of this short introduction, I want to thank all authors for their excellent contribution and their willingness to implement their contribution into the conceptional context of this book. Ms Schoell, I want to thank for her excellent linguistic support.

Biomodulatory therapy approaches, realized in multiple multi-center phase II trials in cooperation with many colleagues, represent the basis for describing tumor systems. These studies could only be carried out with the support of others convinced of the 'alternative' therapy approach in contrast to current emancipatory interests.

The ideas for these novel biomodulatory tumor therapies were based on the intent to palliatively treat systemically pre-treated patients with metastatic tumors. These studies would have been impossible without the tremendous support of a meanwhile retired colleague, Dr. Bross, my colleagues at our and external departments, and various supporters from the pharmaceutical industry: Thank you very much indeed.

I would like to express my gratitude to Dr. Witz for giving me the opportunity to publish in his book series focusing on tumor microenvironment.

The book and its contributions have been conceptionally structured to introduce the reader to evolutionary tumor systems but also to open up perspectives that may be derived from novel systems considerations.

Chapter 2
Tumor Systems Need to be Rendered Usable for a New Action-Theoretical Abstraction: The Starting Point for Novel Therapeutic Options

Albrecht Reichle

Abstract 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. 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. (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. 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 [56].

Keywords Tumor systems • Modularity • Rationalization • Metastatic tumor • Robustness • Personalized tumor therapy • Biomodulatory therapy • Metronomic chemotherapy • Transcriptional modulation

A. Reichle (✉)
Department of Hematology and Oncology, University Hospital Regensburg,
Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany
e-mail: Albrecht.reichle@klinik.uni-regensburg.de

A. Reichle (ed.), *From Molecular to Modular Tumor Therapy*,
The Tumor Microenvironment 3, DOI 10.1007/978-90-481-9531-2_2,

2.1 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 microenvironment [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: 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.

2.2 Methodological Approach

2.2.1 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.

2.2.2 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)
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)**

2.2.3 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 out- lined 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 macrophages. 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 macrophages 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.

2.2.4 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].

2.2.5 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].
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.

2.2.6 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].

2.2.7 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**.**

2.2.8 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].

2.3 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 usable 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].

Denotation and identity of a cell or a cell system. Intercellular 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 assignation 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. 2.1).

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 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. 2.1). 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].

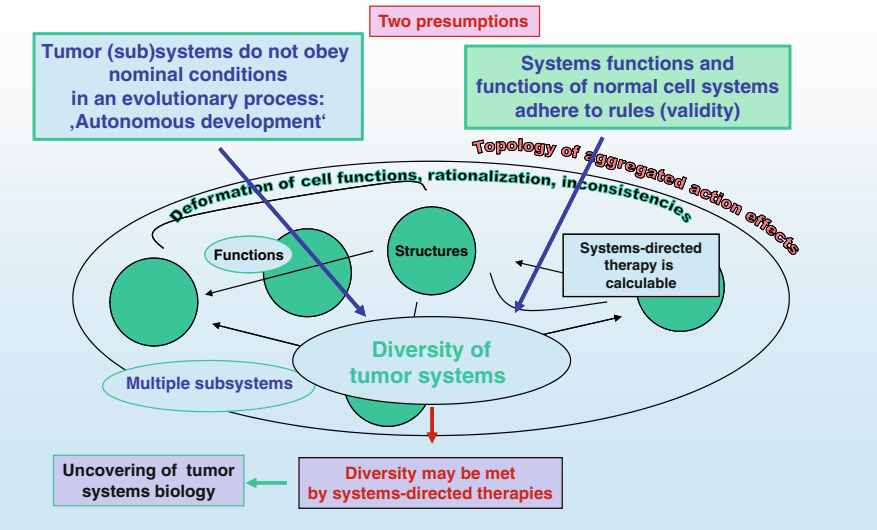


Fig. 2.1 Systems-directed therapies may integrate action-theoretical systems terms (theory) and biomodulatory therapy-derived comprehension (experimental part) of tumor-associated subsystems (e.g. inflammation, angiogenesis…), thereby uncovering and meeting diversity of tumor systems