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Intracellular and intercellular signaling networks in cancer initiation, development and precision anti-cancer therapy. RAS acts as contextual signaling hub

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Abstract

Cancer initiation and development are increasingly perceived as systems-level phenomena, where intra- and inter-cellular signaling networks of the ecosystem of cancer and stromal cells offer efficient methodologies for outcome prediction and intervention design. Within this framework, RAS emerges as a ‘contextual signaling hub’, i.e. the final result of RAS activation or inhibition is determined by the signaling network context. Current therapies often ‘train’ cancer cells shifting them to a novel attractor, which has increased metastatic potential and drug resistance. The few therapy-surviving cancer cells are surrounded by massive cell death triggering a primordial adaptive and reparative general wound healing response. Overall, dynamic analysis of patient- and disease-stage specific intracellular and intercellular signaling networks may open new areas of anticancer therapy using multitarget drugs, drugs combinations, edgetic drugs, as well as help design ‘gentler’, differentiation and maintenance therapies.

Keywords

cancer attractors; cancer stem cells; combination therapies; N=1 trials; RAS; signaling networks

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1. Cancer initiation and development as a signaling network phenomenon

Cancer initiation and development (where the latter also includes the development of metastases) are increasingly perceived as systems-level phenomena, where signaling network descriptions offer an efficient methodology for analysis, outcome prediction and intervention design [1–5]. Signaling pathways (especially in humans [2]) are intricately intertwined by cross-talks forming an elaborate signaling network, which integrates a large number of parallel extracellular stimuli to adequate cellular responses. Nodes of the human signaling network are primarily proteins or microRNAs participating in signaling. In the genetic regulatory network representation (which can be regarded as “extension” of the signaling network) DNA sequences contributing to gene expression are also included as network nodes.

Edges connecting signaling network nodes are activating or inhibitory physical connections of participating proteins, microRNAs and DNA-sequences including enzymatic actions, like phosphorylation, or dephosphorylation [1–5].

During cancer initiation and development, the human signaling network undergoes gross changes in the expression level of nodes, as well as in the sign (activation or inhibition) and weight (strength) of their connecting edges. There are several signaling network resources (such as the curated and multi-layered SignaLink database, <http://signalink.org> [2,5]), among which the Atlas of Cancer Signaling Networks [4] is primarily focused on signaling components important in cancer. Proteins with cancer-related mutations are often hubs of the signaling network, which are becoming enriched in positive regulatory loops during cancer development [6,7].

Incorporation of personalized data, such as mutation, single nucleotide polymorphism, transcriptional, proteome, signalome (e.g. phosphoproteome) and epigenetic profiles to signaling networks significantly enhance patient- and disease stage-specific drug targeting in anti-cancer therapies [1–5,8,9]. Patient specificity can differentiate network behavior in at least four different levels: A.) at the level of the genetic background (e.g., single-nucleotide polymorphisms and cancer-related mutations, copy-number changes or chromatin rearrangements); B.) at the level of gene expression and translational changes (caused by e.g. transcriptional, epigenetic, microRNA or signaling mediated changes); C.) at the level of the microenvironment (e.g. neighboring cells, tissue structure, etc.); and finally D.) by exogenous signals (e.g. nutrients or drugs). All provide increments to the patient-specific, context-dependent responses to anti-cancer therapy [8–10].

The plethora of intercellular interactions between members of the highly heterogeneous cancer cell community, as well as the surrounding stromal cells, emerge as key elements of our understanding of the evolution of cancer. This delicate intercellular network has a complex cooperation (and competition) pattern of participating cells, which continuously evolves as cancer develops [11,12]. These changes include the “transformation” steps of stromal cells, e.g. of fibroblasts, where the original inhibition of cancer growths switches to cancer activation [13,14]. Similar transformation steps accompany the metastatic process

[15,16]. Several contributions of the current issue contain important details of the involvement of cell-cell interactions in cancer initiation and development.

Besides the assessment of signaling network structural details, the analysis of network dynamics is an essential key to understand the functional outcome of cancer-induced molecular changes, as well as to achieve efficient intervention design. *Reka Albert* and coworkers were among the first to describe a functional Boolean model of cancer-specific ‘survival-network’ using large granular lymphocytic leukemia cells [17]. Their work was followed by a more extensive Boolean dynamic model of cancer-specific signaling network [18]. The seminal work of *Stuart Kauffman*, *Sui Huang* and *Ingemar Ernberg* [19] convincingly argued that cancer cells are trapped in abnormal attractors named as cancer attractors. A recent study [20] showed that subpopulations of cancer cells may re-populate the attractor-basin. Importantly, ‘edge-cells’ (i.e. cancer cells having signaling network activation pattern situating them at the edge of the cancer-attractor basin) may jump to an adjacent attractor, which may represent an even more de-differentiated, aggressive or metastatic state. Increased noise accelerates this process [20,21]. Recent work developed an efficient simulation tool of signaling network dynamics, Turbine [21,22, <http://turbine.ai>], which is able to find cancer attractors and to determine multitarget intervention point sets shifting cancer cells from their abnormal attractors to attractors characterizing healthy cells and/or driving cancer cells to apoptosis.

Contributions to this special issue focus on the RAS protein family, which serves as a key signaling hub of cancer initiation and development. From the papers of the issue RAS emerges as a contextual signaling hub, whose final action heavily depends on the intracellular and intercellular signaling network context. Understanding RAS-related signaling circuits and other key, cancer-specific signaling changes offers novel anticancer targets and prognostic markers.

2. RAS as a contextual hub of signaling networks in various stages of malignant transformation

This issue is centered on the contribution of RAS proteins to cancer initiation and development. RAS is a small GTPase, which is at the cross-road of a number of signaling pathways that regulate key cellular functions. Mutations in the *RAS* gene family of proto-oncogenes are very common, being found in 20% to 30% of human tumors and in over 90% of pancreatic cancers. Despite our knowledge of the mechanisms behind the regulation of RAS activity, the outcome of various RAS-based anti-cancer therapies have been less than satisfactory, which has led to the characterization of RAS as an “undruggable” protein [23,24].

In the opening contribution of this special issue series, *Channing Der* and co-workers summarize the role of wild type RAS isoforms in cancer [25]. They conclude that role of wild type RAS proteins in oncogenesis, tumour maintenance and metastasis is context-dependent. On one hand, wild type RAS proteins are likely to serve as tumour suppressors when the mutant RAS is of the same isoform. On the other hand, the preponderance of evidence indicates that wild type RAS proteins play a tumour promoting role when the

mutant RAS is of a different isoform. In the absence of mutant RAS, RAS is recognized as a mediator of oncogenic signaling due to chronic activation of upstream receptor tyrosine kinases that feed through RAS. Moreover, in these cases activation of wild type RAS may drive cancer upon the loss of negative RAS regulators, such as NF1, GAP or SPRY proteins [24–26]. *Michael Ohh* and co-workers [27] describe the structural and functional aspects of RAS regulation by non-receptor tyrosine kinases and phosphatases focusing on the structural details of SRC- and SHP2-mediated changes and related anti-cancer therapeutic options [28,29].

Adding to the complexity of RAS-related signaling events, *Ruth Nussinov* and co-workers [30] propose that there are two independent pathways in tumor proliferation centered on either MAPK/ERK and PI3K/AKT/mTOR or activating YAP1 and MYC. While the first pathway is related to KRAS, the second involves WNT/ β -catenin, Notch and Hedgehog pathways. These two pathway sets can substitute each other and amplify each other, if activated simultaneously promoting proliferation. This analysis suggests, that successful therapeutic interventions must inhibit multiple pathways at the same time [31,32]. As another key example of RAS-centered signaling network cross-talks, *Geoffrey Clark* and co-workers [33–35] summarize our current knowledge on RASSF family with six core scaffolding RASSF proteins that contain conserved RAS-association domains. Besides the involvement of RASSF members in pro-apoptotic signaling pathways, such as BAX and Hippo, RASSF proteins can also connect RAS to a surprisingly broad range of signaling pathways that control senescence, microtubule dynamics, protein turnover, inflammation, autophagy and DNA repair. From the network standpoint, the frequent epigenetic inactivation of RASSF genes in human tumors disconnects RAS from all these pro-apoptotic and other signaling systems, enhancing RAS driven transformation and metastasis.

As the starting contribution of the three papers of this issue describing the complexity of the RAS-centered signaling network, *Boris Kholodenko* and co-workers [36] delineate the intricate dynamic control and plasticity of RAS-to-ERK signaling including feedback-activation, noise-rejection, ultrasensitivity, integral feedback, negative feedback amplification and perfect adaptation both at the single cell level and in a cell population context. They convincingly argue that this complexity can be tackled only by using mathematical models of network dynamics leading to the development of dynamically fine-tuned, rational cancer therapy design [37,38]. Genomic tools, such as the assessment of RAS signaling network-related mutations, DNA-copy numbers, DNA-methylation, gene expression and proteome patterns summarized by *Andrea Bild* and co-workers [39–41], help to capture the complexity of RAS signaling. These genomic approaches enable the design of personalized, high-precision anti-cancer therapies, as well as the “real-time” assessment of the development of drug resistance mechanisms. In the closing contribution of the three signaling network-related approaches *David Gutmann* and co-workers [42–44] use the Neurofibromatosis type-1 (NF1) cancer predisposition syndrome as an illustrative platform to show how RAS/NF1 signaling can create functional diversity both at the cellular and tissue levels. The NF1 protein (neurofibromin) is a RAS GTPase activating protein, thus its defect induces RAS hyper-activation. However, its impact is highly context-dependent exhibiting a wide range of clinical variability. Gutmann’s and co-workers’ description of cell-type and tissue-specific differences in molecular composition of RAS/NF1-related

signaling complexes, as well as of the contextual effects of multiple extracellular effectors [42] introduces the next level of complexity in cancer initiation and development: the cell-cell interactions of the cancer and stromal cell ecosystem described in the next section in detail.

3. The role of inter-cellular signaling in cancer initiation and development

Tumors have an extremely heterogeneous population of cancer cells, which continuously evolve [45]. Cancer stem-like cells display extremely efficient adaptive responses to changes in the tumor environment including therapeutic interventions. This extremely large evolvability of cancer stem-like cells can be reflected in the shifts between highly plastic behavior (and the corresponding fuzzy network structures) characterized by rapid proliferation and a more rigid behavior (and the corresponding hierarchical, well-defined network structures) characterized by quiescence, asymmetric cell division and increased invasiveness [46]. This rapidly changing duality represents a general mechanism of learning and adaptation [3,47] and corresponds well with the defining hallmarks of cancer stem cells: the possession of the capacity to self-renew, and to repeatedly re-build the heterogeneous lineages of cancer cells that comprise a tumor in new environments [46].

In addition to cancer cells, there is a large variety of stromal cells, such as fibroblasts, macrophages, lymphocytes, etc., which increase tumor heterogeneity further. Several surrounding cells, such as fibroblasts, initially inhibit tumor formation. However, later they become transformed by the developing cancer cells, and in this transformed state they fail to inhibit cancer cell proliferation. Recent studies showed that in the transformation of cancer-associated fibroblasts, the RHO-proteins, related members of the RAS superfamily of small GTPases, plays a key role [13,14].

Cancer cells and associated stromal cells form a complex cellular ecosystem, which has a large number of intricate cooperative (and competitive) interactions. The elucidation and mathematical modeling of this complexity while only beginning [11,12], may be crucial for developing anti-cancer therapies, which have a higher chance to circumvent drug resistance, than most of the 'homogeneous cell population-based' therapeutic approaches used today. A recent paper convincingly showed that oncogenic KRAS (having the mutation of G12D) plays a key role establishing reciprocal signaling between cancer cells and stromal fibroblasts of pancreatic ductal adenocarcinoma. Associated fibroblasts help to increase cancer cell mitochondrial capacity by IGF1R/AXL-AKT signaling [48]. Another recent example of cancer cell cooperation was observed in the development of brain metastases of human and mouse breast and lung cancer cells, where gap junctions transfer cGAMP (cyclic-GMP-AMP dinucleotide) from carcinoma cells to astrocytes. cGAMP induces the release of inflammatory cytokines from astrocytes activating STAT1 and NF- κ B in metastatic carcinoma cells supporting tumor growth and chemoresistance. Orally bioavailable gap-junction inhibitors can break this paracrine loop [49]. Importantly, metastatic cells are often migrate as cell communities, where cooperative interactions both between cancer cells themselves, as well as between cancer cells and stromal cells help migration and the metastatic process [50,51].

Besides hypoxia and the consequent acidity, one of the key components of tumor microenvironment is inflammation. *David Barbie* and co-workers [52–54] describe the involvement of inflammation (as well as its major components: NF- κ B, STAT3 and secreted cytokines, such as IL6) in the activation of KRAS signaling inducing a variety of survival pathways, such as MAPK signaling and autophagy. The authors have highlighted the importance of targeting inflammation early in the course of tumor development (such as the effect of COX2 inhibition by aspirin or other non-steroidal anti-inflammatory agents hindering colorectal cancer development [55]).

Mircoorganisms, including the important contribution of microbiota, influence both local and systemic inflammation. Disruption of the gut microbiota impairs the efficiency of immuno- and chemotherapies [56]. In the closing contribution of this special issue *Ruth Nussinov* and co-workers [57–59] explore a highly exciting special area of cell-cell interactions: the mimicry of host protein binding surfaces by pathogenic proteins. This mimicry leads to the rewiring and repurposing of the host signaling pathways contributing to carcinogenesis including the modulation of RAS-signaling.

4. Intracellular and intercellular signaling network-based precision anti-cancer therapy

President Nixon launched a “war against cancer” in 1971. Indeed, the war metaphor describes rather well many of the current anti-cancer therapeutic approaches using powerful destructive forces to kill cancer cells. The drawbacks of this approach are summarized in the key review of *Sui Huang* [60]. 1.) Several treatments severely damage healthy cells causing large side- and adverse effects. 2.) Specifically targeted interventions may (partially) circumvent this problem, but while inhibiting one cancer hallmark may often activate another, like the angiogenesis inhibitors, which led to an increased rate of metastasis [15]. 3.) Crucially, the extreme plasticity of cancer cells, and especially that of cancer stem-like cells enables them to shift to dormancy as one of the responses to anti-cancer treatment often seeking the protection of a special niche of stromal cells [47]. Following the therapeutic intervention these quiescent cells may shift back to proliferation occupying a new, ‘rebellious’ cancer attractor [60] and/or develop drug resistance. 4.) Worst of all: the few surviving cancer cells are surrounded by massive cell death, which triggers a primordial adaptive and reparative wound healing response alongside the increase of ‘cell stemness’ [60,61]. Some of the key molecular mechanisms helping this generalized wound healing response are the activation of the WNT-pathway, and the release of alarmins stimulating inflammation [60,62,63].

Combination therapies and multitarget drugs designed by the dynamic network analysis of cancer-related signaling networks - shifting cancer cells from cancer attractors [19,20] to apoptosis - may overcome some of the problems listed above [3,21, <http://turbine.ai>]. Importantly, this analysis may be extended to the intercellular signaling networks of the cancer/stromal cell ecosystem, which may form cancer tissue attractors [19,64,65]. As one example out of many, the simultaneous inhibition of proliferation pathways and the generalized wound healing response described above (e.g. by inhibiting the WNT pathway

[63]) may be an efficient approach. Alternatively (or simultaneously), using edgetic drugs (aiming to block specific signaling protein-protein interactions [66]), targeting stromal cells [48,67] or designing gentler, differentiation and/or maintenance therapies [68] may also offer novel therapeutic interventions. The spread of N=1 trials [69] using a personalized, ‘on-line’ omics-status of several samples of the patient’s heterogeneous tumor cells enable patient- and disease stage-specific therapies [1–5,8,9].

5. Conclusions and perspectives

Our short summary and the papers of this special issue [25,29,30,33,36,39,42,52,57] highlight the promises and challenges of using signaling networks (including RAS-related signaling events) in the description of cancer initiation and development, metastasis and the emergence of drug resistance. As key messages we emphasize that

1. the RAS proteins emerges as a contextual signaling hub, i.e. the final result of RAS activation or inhibition is determined by the intracellular and extracellular signaling network context;
2. following conventional therapies the partially non-genetic, dynamic heterogeneity of cancer cell population induces the replenishment of the cancer attractor with surviving cells. This may lead to surviving cells shift to a novel attractor, which has increased metastatic potential and drug resistance. The few surviving cancer cells may now be surrounded by massive cell death, which triggers a primordial adaptive and reparative general wound healing response alongside the increase of ‘cancer cell stemness’;
3. the ‘therapy-induced training’ of cancer cells to develop increased invasiveness and drug resistance described above is further complicated by interactions of the cancer/stromal cell ecosystem and its microenvironment;
4. the dynamic analysis of patient- and disease-stage specific intracellular and intercellular signaling networks may open new areas of anticancer therapy using multitarget drugs, combination therapy, edgetic drugs and neutralization of the emerging general wound healing response, as well as designing gentler, differentiation and maintenance therapies.

The approaches outlined above and in the contributions of this special issue [25,29,30,33,36,39,42,52,57] may overcome the current Nietzschean dilemma of cancer cell targeting: “what does not kill me makes me stronger” [60].

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