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Mini review

Network-based approaches for drug response prediction and targeted therapy development in cancer

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ABSTRACT

Signaling pathways implicated in cancer create a complex network with numerous regulatory loops and redundant pathways. This complexity explains frequent failure of one-drug-one-target paradigm of treatment, resulting in drug resistance in patients. To overcome the robustness of cell signaling network, cancer treatment should be extended to a combination therapy approach. Integrating and analyzing patient high-throughput data together with the information about biological signaling machinery may help deciphering molecular patterns specific to each patient and finding the best combinations of candidates for therapeutic targeting. We review state of the art in the field of targeted cancer medicine from the computational systems biology perspective. We summarize major signaling network resources and describe their characteristics with respect to applicability for drug response prediction and intervention targets suggestion. Thus discuss methods for prediction of drug sensitivity and intervention combinations using signaling networks together with high-throughput data. Gradual integration of these approaches into clinical routine will improve prediction of response to standard treatments and adjustment of intervention schemes.

1. Introduction

Initiation and progression of cancer involve multiple molecular mechanisms. In addition the diversity across tumors from different patients and even across cancer cells from the same patient makes the picture very complex. The aim to find a common mechanism for therapeutic targeting of cancer becomes thus unpractical [1]. Therefore the idea of 'personalized' or 'precision' medicine has been suggested, aiming to find tailored treatment regimen for each patient according to the individual genetic background and tumor molecular profile [2] [3]. This attempt is achievable thanks to sufficient molecular characterization of cancers accumulated using high-throughput technologies [4]. However, despite availability of cancer high-throughput data, they are not fully exploited to provide the clue on deregulated mechanisms that would guide to specific treatment. Indeed, the most advanced schemes of targeted cancer therapies that do make use of high-throughput data, are based on detection of molecular abnormalities for several known genes determined as drivers or biomarkers of a given disease, that is followed by matching of treatment from the available drug panel [5]. In this approach majority of information embedded in the high-throughput data profiles are not considered, which narrows down the spectrum of putative targets. Taking into account the information about biological signaling machinery in cells may help to better interpret the patterns observed in high-throughput data of tumors. This will allow rationalized medicine approach for drug response prediction and personalized treatment assignment [6] [7] (Fig. 1).

2. Cancer high-throughput data signatures and drug response predictors

Generations of big amount of high-throughput data for different types of cancer allowed system-level analysis. Several cancer-type specific signatures and classifiers were proposed based on

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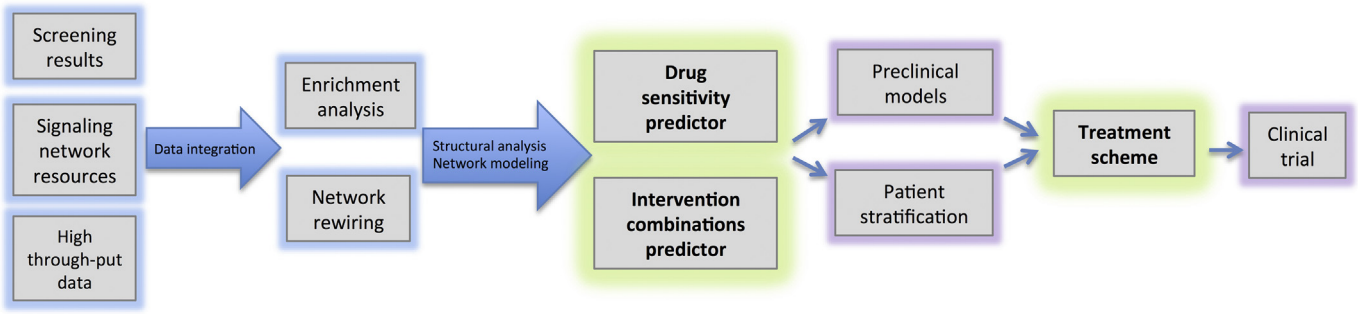

Fig. 1. Rationalized cancer medicine workflow: from computational systems biology approach to integration in clinics.

genomic [8], miRNA [9], mutational [10], methylation [11] and gene expression [12] data. In addition, the signatures associated with clinical profile containing treatment response information, lead to appearance of response predictors to standalone drugs. Among many, there are breast cancer PAM50, MammaPrint, NanoString, OncotypeDX predictors that are used in clinics [13]. To undercover molecular mechanisms associated with the phenotype of the disease, functional interpretation of high-throughput data-based signatures is often done using GO terms or pathway resources such as STRING [14], BioGRID [15] or using compilations of many databases together, such as PathwayCommons [16] or ConsensusPathDB [17] (Table 1). To achieve meaningful functional interpretation of data using those databases, number of gene set enrichment methods were developed [18]. Among others, Gene Set enrichment analysis (GSEA) using biological pathways and high-throughput data helps to understand molecular processes implicated in the disease [19]. More global systematic enrichment analysis of cancer high-throughput data, using IPAD resource, helps revealing not only enriched signaling pathways but also associations between the patient data and various parameters as disease type, drug specificity and organ specificity, collectively allowing to classify patients and figure out drug susceptibility [20]. More advanced concordant integrative gene set enrichment analysis takes into account multiple expression data sets and pathways resources for consolidation of enriched processes in different cancers and suggestion of deregulated mechanism for therapeutic intervention [21] (Table 2). However it emerged lately that drug response prediction based only on signatures and enrichment studies requires further refinement supported by knowledge on molecular interactions and signaling network topology [22].

3. Signaling network and high-throughput data for deciphering a molecular footprint of cancers

Signatures and functional enrichment studies using pathways databases are suitable for stratifying cancers and understanding what molecular mechanisms are implicated in various cancer types, but these approaches still do not provide the clues on mechanistic basis of the disease and do not address the question of signaling network rewiring during cancer initiation and development. The step forward is to use molecular information detailed in pathways and signaling network resources as Panther [23], Spike [24], Kegg Pathway [25], Reactome [26], ACSN [27] (Table 1). These resources provide a more global picture of cell signaling with sufficient granularity of molecular detail description, capturing crosstalks and feedback loops between molecular circuits. Analysis of high-throughput data in the context of this type of networks allows better functional interpretation and verification of redundant mechanisms taking into account the network topology (discussed below).

To grasp the general trends of data distribution across cell molecular mechanisms represented on the signaling networks, visualizing high-throughput data in the context of biological networks is essential step. There are number of tools for data visualization on

Table 1
Interactiome and cell signaling resources.

Name	Website	Description	Reference
Signaling pathways and networks resources			
STRING	http://string-db.org	Integrated protein–protein interaction daatabase	[14]
BioGRID	http://thebiogrid.org	Integrated protein–protein and genetic interaction daatabase	[15]
PathwayCommons	http://www.pathwaycommons.org	Biological pathways resource collected from public pathway databases	[16]
ConsensusPathDB	http://consensuspathdb.org	Integrated resource of interaction networks and pathways	[17]
Panther	http://pantherdb.org	Collection of biological pathways and data visualization and analysis tools	[23]
Spike	http://www.cs.tau.ac.il/~spike	Collection of curated, peer reviewed pathways and data visualization tools	[24]
KEGG Pathway	http://www.genome.jp/kegg/pathway	Collection of manually drawn pathway maps visualization tool	[25]
Reactome	http://www.reactome.org	Collection of curated, peer reviewed pathways and data visualization/analysis tools	[26]
ACSN	http://acsn.curie.fr	Collection of curated, peer reviewed, interconnected cancer-related signaling networks and data visualization/analysis tools	[27]
Interactomes and drug response resources			
DrugBank	http://drugbank.ca	Integrated drug and drug target information resource	[40]
STITCH	http://stitch.embl.de	A chemical–protein interaction database to query chemicals or proteins for their known	[41]
KEGG Drug	http://genome.jp/kegg/drug	Integrated drug and drug target information resource	[42]
Cancer Therapeutics Response Portal	https://www.broadinstitute.org/ctrp/	Drug sensitivity in cell lines database	[43]
Kinome NetworkX	http://bioinfo.mc.vanderbilt.edu/kinomenetworkX	A global human kinome interaction map	[49]
NCGC pharmaceutical collection	https://tripod.nih.gov/npc	Collection of approved and investigational drugs and drug interactions	[50]

Table 2
Tools for network-based analysis of intervention combinations and drug response prediction.

Name	Website	Description	Reference
GSEA	www.broadinstitute.org/gsea	A computational method that determines whether an a priori defined set of genes shows statistically significant, concordant differences between two biological states	[19]
IPAD	http://bioinfo.hsc.unt.edu/ipad	A computational method for enriched signaling pathways calculation and finding associations between disease type, drug specificity, organ specificity and patient clinical data	[20]
PathCards	http://pathcards.genecards.org	Systemic multisource of consolidated pathways and tools	[44]
iCTNet	http://www.cs.queensu.ca/ictnet	iCTNet: a Cytoscape plug-in to construct an integrative network of diseases, associated genes, drugs and tissues	[45]
DAISY		Search for synthetic lethal pairs (SL) and synthetic dosage lethal pairs (SDL) using co-expression, and counter-selected genes co-inactivation in data and shRNA screens.	[47]
DrugComboRanker		Drug combinations predictor by identifying drugs whose targets are enriched in the disease network	[51]
DIAMOnD		Network topology-based approach to elucidate the molecular mechanisms of human disease	[54]
KEGG-PATH		Method to estimate the impact of different players of KEGG pathways into the output, taking into account pathway hierarchy and structure	[55]
OCSANA	http://bioinfo-out.curie.fr/projects/ocsana/OCSANA	Method for network-based prediction of intervention combinations to disrupt a phenotype	[56]

networks, among others there are ReactomeFiViz [28], KEGG Mapper [29], iPAth [30], Medusa [31] and NaviCell [32] [33] (Table 3). The data visualization at different zoom levels of signaling can be also helpful for assessment of patterns, structures and functional modules on the networks deregulated in the disease, that can guide in narrowing down the areas of interest for further detailed study of the mechanisms.

4. Synthetic lethality paradigm and resistance to drugs

The numerous molecular mechanisms deregulated in cancers and the complexity of signaling network demonstrate that drug resistances observed in many cases can be anticipated and explained by signaling network robustness. To overcome the resistance, the synthetic lethality (SL) approach has been introduced into the cancer treatment schemes.

The classical paradigm defines synthetic lethal interactions as a combination of two or more gene deletions that significantly affects cell viability, whereas single deletion of each one of those genes does not. SL treatment approach in cancer takes an advantage of vulnerabilities in tumor cells which display abnormal expression or function of one gene from synthetic lethal sets. Targeting synthetic lethal partner allows selective killing of tumor cells [34]. This therapeutic approach is applied in BRCA mutated breast cancers using PARP inhibitors, although there are frequent escape from the treatment, requiring to more complex solution [35]. Resistance of breast cancer to the HER2 inhibitor Herceptin is acquired due to the activation of the compensatory Akt-induced glycolytic pathway or Bcl-2-mediated anti-apoptotic pathway [36]. Network reprogramming and re-activation of pathways in cancer via alternative players also create conditions for drug resistance, as in the case of MEK1 inhibition by GSK1120212 in triple negative breast cancer, the resistance to the treatment is due to the activity of MEK2 that re-activates MAPK pathway [37]. Another way of resistance development is activation of non-related pathways that initiate favorable conditions for cancer propagation and metastasis. This phenomenon has been observed in treatment of renal cell carcinomas by the combination therapy via inhibition of VEGFR and mTORC1 that lead to compensatory mTORC2-mediated Akt and hypoxia-inducible factor-1 (HIF-1) activation and eventually angiogenesis ameliorating metastatic development [38]. These examples demonstrate that the reasons for classical SL pair-based treatments failure is signaling network robustness ensured by (1) Redundant mechanisms that provide the possibility to bypass the drugs effect or (2) Compensatory players that re-activate inhibited pathways or (3) Turning on non-related, but favorable molecular mechanisms supporting disease progression, basically representing an example of side-effects. Therefore, the ways for identifying and blocking those active pathways and players should be found to overcome not only drug resistance, but also the side effects. To achieve this aim, more complex approach of intervention should be proposed involving targeted combination of drugs.

5. Experimental approach for synthetic lethal combinations identification

Identification of SL pairs in cancer can be addressed using experimental approaches as knockout cells or animal models. More systematic approach consists in high-throughput screening of synthetic lethality using siRNA, shRNA, CRISPR/Cas9 technologies. A sub-set of these methods is gene-drug synthetic lethality screening aiming to retrieve gene-sensitizers for the drug. Those studies lead to generation of SL gene–gene and gene-drug databases and networks [39]. However, experimental methods are time and resources consuming and can cover only limited number of SL pairs. Another significant drawback of these approaches is that they address only pairwise SL interactions. Since signaling pathways create a complex network, the approach should be extended to the SL combinations paradigm, addressed by computational methods.

Table 3
Tools for visualization of high-throughput data in the context of signaling networks.

Name	Website	Description	Reference
KEGG Mapper	http://www.kegg.jp/kegg/mapper	KEGG database-associated tool for data visualization and analysis in the context of pathway maps	[25]
ReactomeFiViz	http://wiki.reactome.org/index.php/Reactome_FI_Cytoscape_Plugin	Cytoscape plugin for data integration into signaling networks	[28]
iPAth	http://pathways.embl.de	Web-based tool for data visualization in the context of pathway maps	[30]
Medusa	http://coot.embl.de/medusa	Tool for data visualization in the context of signaling network and network clustering	[31]
NaviCell	http://navicell.curie.fr	Web-based tool for heterogeneous data visualization and analysis in the context of signaling networks	[32,33]

6. Predicting drug response using network-based approaches

6.1. Interactomes applied for drug response prediction

Accumulated knowledge on SL interactions from SL screens, collections of drugs against human diseases [40], protein druggability data, protein–protein, protein-drug and gene interaction networks [41] [42] [43] can support drug response prediction. To make use of information from those interactomes, several integrated resources were developed, as PathCards, a systemic multisource of consolidated pathways and tools [44] or iCTNet: a Cytoscape plug-in to construct an integrative network of diseases, associated genes, drugs and tissues [45].

The following examples demonstrate the role of interactomes in prediction of SL combinations and suggestion of drug combinations. The meta-analysis of rare somatic mutations across cancers in the context of network identifies vulnerable points in pathways and protein complexes representing potential targets combinations [46]. Network-based approach for systematic cancer mutations stratification reveals non-intuitive combinations of synthetically interacting molecular mechanisms. Using a genome scale, data-driven approach for the identification of cancer SL (DAISY) the comprehensive SL networks were retrieved for different cancers [47]. Alternative method infers drug sensitivity from assessment of pathways activation levels based on multiple data integration into pathway maps [48]. Kinome NetworkX, a global human kinome interaction map has been constructed by integrating kinase-substrate, kinase-drug, protein–protein interactions collectively creating a comprehensive resource for inferring druggable combinations of kinases [49].

To rationalize re-purposing of approved drugs, the comprehensive collection of drugs for human diseases [50] analyzed together with cancer high-throughput data in the context of pathways databases has been done using DrugComboRanker tool [51] suggesting unexpected drug combinations among the available panel of approved drugs that were never used for cancer treatment.

These studies using interactomes together with signaling pathways databases allow to suggest more complex treatments schemes based on knowledge of relationship between molecular players in cell and taking into account the vulnerabilities of tumors inferred from high-throughput data (Table 2 and extensively reviewed in [52]).

6.2. Topology and structural analysis of networks for drug response prediction

Cancer cells are present in a particular cell signaling network state provoked by oncogenic mutations and other molecular abnormalities that sustain cell viability and motility. To tackle the disease, this state of signaling network should be perturbed. The aim is to find the optimal SL interactions, which would shift the state of the signaling network from unfavorable (e.g. drug resistance, proliferation) toward the desired phenotype (e.g. sensitivity to drug, cell death). In addition, to overcome resistance to treatment, interfering with the signaling network at several points simultaneously is necessary. Considering the topology of signaling networks and studying network perturbations together with high-throughput data can guide in prediction of sensitivity to drugs and choice of a correct combination of targets for each patient.

In the first approach, the topology of the network nodes is used to prioritize targets. Perturbation of “hubs”, nodes than have a higher than average number of edges, have an important impact on the network because of their influence on many processes. Complementarily, “bottlenecks” are nodes with high betweenness-centrality, they condition the interactions between modules and their perturbation can decouple such interaction, which are often responsible for drug resistance [53]. These candidates for interference by treatment can be attractive, especially if specifically involved in driving a particular cancer type or deregulated in a given patient. For example, the DIAMOnD algorithm is based on those principles, assesses neighborhood of deregulated genes, to retrieve SL combinations [54]. However interference with those central players often leads to major effect at the level of the whole signaling, therefore the consequent side effects and toxicity should be anticipated and addressed.

In the second approach, the global network topology is used for integration of cancer high-throughput data into signaling networks and finding the network targets dictating the phenotype in the disease. For example, applying “guilt by association” principle assuming interaction partners have similar roles, including involvement in pathologies. This can be true for components in the same functional complex, co-regulators of a reaction or nodes interacting with many differentially affected players in the network between pathological and normal cells. Defining a “field of influence”, the distance in the vicinity of the deregulated node, where players are assumed to have the similar impact on the pathology, is a source of potential targets for interference. Exploiting the notion of “network distance” between proteins, namely if several affected proteins create a compact group when mapped on the signaling network and therefore can be related functionally, they may represent together a set for intervention [27].

In the third approach, path analysis of signaling networks helps listing molecular mechanisms through which an effect can propagate in the network to achieve the phenotype. Finding intervention points along those paths to interfere with the phenotype, helps to suggest synthetically interacting sets of genes (or synthetic lethal sets).

The aforementioned principles are lying in the basis of tools as KEGG-PATH that allows to estimate the impact of different players of KEGG pathways into the output taking into account hierarchy, pathway structure and correlations between different pathways [55]. To address the problem of redundant pathways in signaling network, several algorithms for calculating minimal intervention sets have been developed. For example, OCSANA method allows to predict which combination of interventions should be applied to network to disrupt a signal leading to the particular outcome. Thus high-throughput data can be integrated for scoring and selecting optimal synthetic lethal sets in each particular patient, exploiting the specific vulnerabilities [56]. These and other topology-based methods for structural analysis of maps are used for retrieving intervention combinations in cancer and predicting response to treatment (Table 2 and extensively reviewed in [57]).

Studying properties and rewiring of networks in different types of cancers helps figuring out what specific mechanisms are associated with each disease. In this case, mathematical modeling of network can be applied. For example, disease-specific gene expression network rewiring study helped to reveal unique sets of proliferation regulators in lung adenocarcinoma that represent the intervention targets [58]. Data-driven mathematical modeling using fuzzy logic approach predicts kinase signaling network rearrangements in melanoma cells and explains response to combinations of kinase inhibitors [59]. The advanced method for perturbation points finding using Boolean modeling and also taking into account the degree of inhibition by drug allows finding disease/drug matching and leading to more specific intervention sets suggestion [60].

Finally, prediction of drug sensitivity based on higher organization of networks, at the level of functional modules, can provide more robust results. For example, the dynamical reorganization of functional modules in the molecular interaction networks upon

treatment was studied using transcriptional profiling and hierarchical network structure analysis, allowing to associate network status to the drug sensitivity in patients [61]. The combination of machine learning and graph theory can be used on integrated network of human gene interactions (INHGI) and oncogenes resources to predict the oncogenic potential of interactions and retrieve cancer-related signaling sub-networks suitable for intervention [62].

7. Summary

We have described three major strategies for drug response prediction using networks analysis that helps in designing more properly the unique drug targets combination: (1) High-throughput data-based signature retrieval; (2) Inferring intervention points from integrated analysis of interactomes and (3) Interference set finding using topological analysis of networks and mathematical modeling of network rewiring.

Applying network-based methods will allow to reason on intervention schemes at the level of the whole cell signaling and to take into account specific vulnerabilities in tumors of each patient [63]. Development of robust pipelines providing various methods for prediction of drug response and suggestion of intervention schemes will ameliorate patient-specific treatment.

Transparency document

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