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Network-based cancer precision medicine: A new emerging paradigm

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ABSTRACT

The complex interactions in biological systems have been shown to affect the response to single-targeted therapies which were initially developed under the "reductionist paradigm" of cancer precision medicine. To address these fundamental challenges, great efforts have been dedicated from a network perspective to explore the mechanisms underlying tumorigenesis and progression and to extend our understanding of cancer as a complex disease, which is exploiting new advances in cancer diagnosis, prevention, and treatment. This review summarizes recent progress of network applications in cancer precision medicine research, including biomarker identification, cancer patient stratification and network target recognition, highlights network-based systematic integrations across macro and micro networks, and discusses the tremendous potential of this new emerging network-based "systems paradigm" for precision medicine, which would ultimately make substantial progress for fighting cancer.

1. Introduction

Advances in molecular characterization of cancers have made it clinically feasible to tailor personalized anti-tumor therapies. Successful examples including imatinib for BCR-ABL-positive chronic myeloid leukemia [1], trastuzumab for HER2-positive breast cancer [2] and gefitinib for EGFR-positive non-small-cell lung cancer [3] have demonstrated the power of this approach. However, a relatively small proportion of patients with driver mutations were benefited from precision therapies in several recent large clinical trials [4–6], and the response rates of immune checkpoint inhibitors which generated complete responses in advanced melanomas are modest across tumor types [7,8].

Various factors may contribute to the limited success of current evaluations of cancer precision medicine: 1) Molecular aberrances observed with tumorigenesis are often interpreted independently of each other level and out of context of biological networks, which impedes forming a comprehensive understanding of oncogenesis mechanisms [9]. 2) Although often used to stratify pathologically identical patients, tumor mutation profiles are so sparse that it is common for patients to share no more than one single mutation [10], which impedes the designs of randomized clinical trials. 3) Differences between tumor-types in the underlying molecular mechanisms may account for the dramatic decline of the response rate for some therapies, such as the BRAF (V600E) inhibition in colon cancer [11]. 4) Molecular characterization of sequential biopsy samples from tumor sites in the same patients show spatial and temporal heterogeneities [12], which makes the benefits of single-targeting agents limited. Additionally, current cancer research provides limited contributions to cancer prevention which had not received sufficient scientific focus until recently [13] while could reduce 70% cancer death around the world [14].

Great efforts have been devoted to address above challenges of the "reductionist paradigm" of cancer precision medicine. As one of the emerging promising strategies, network-based approach has attracted increasing attentions, since it could capture the systemic nature of complex diseases by simplifying biological entities and interactions as nodes and edges and facilitating the integration of phenomics, genomics, transcriptomics, epigenetics and other omics [15,16]. And this transition from the single-alteration perspective to the network-based paradigm would ultimately make substantial progress for cancer diagnosis, prevention, and treatment [17]. In this review, we illustrate fundamental concepts of network science, summary successes and challenges when applying network approach to cancer research and discuss systematical integrative strategies for network-based cancer precision medicine.

2. Network basics in cancer precision medicine

Network-based approaches are powerful tools to elucidate pathophysiological mechanisms involved in the occurrence and progression

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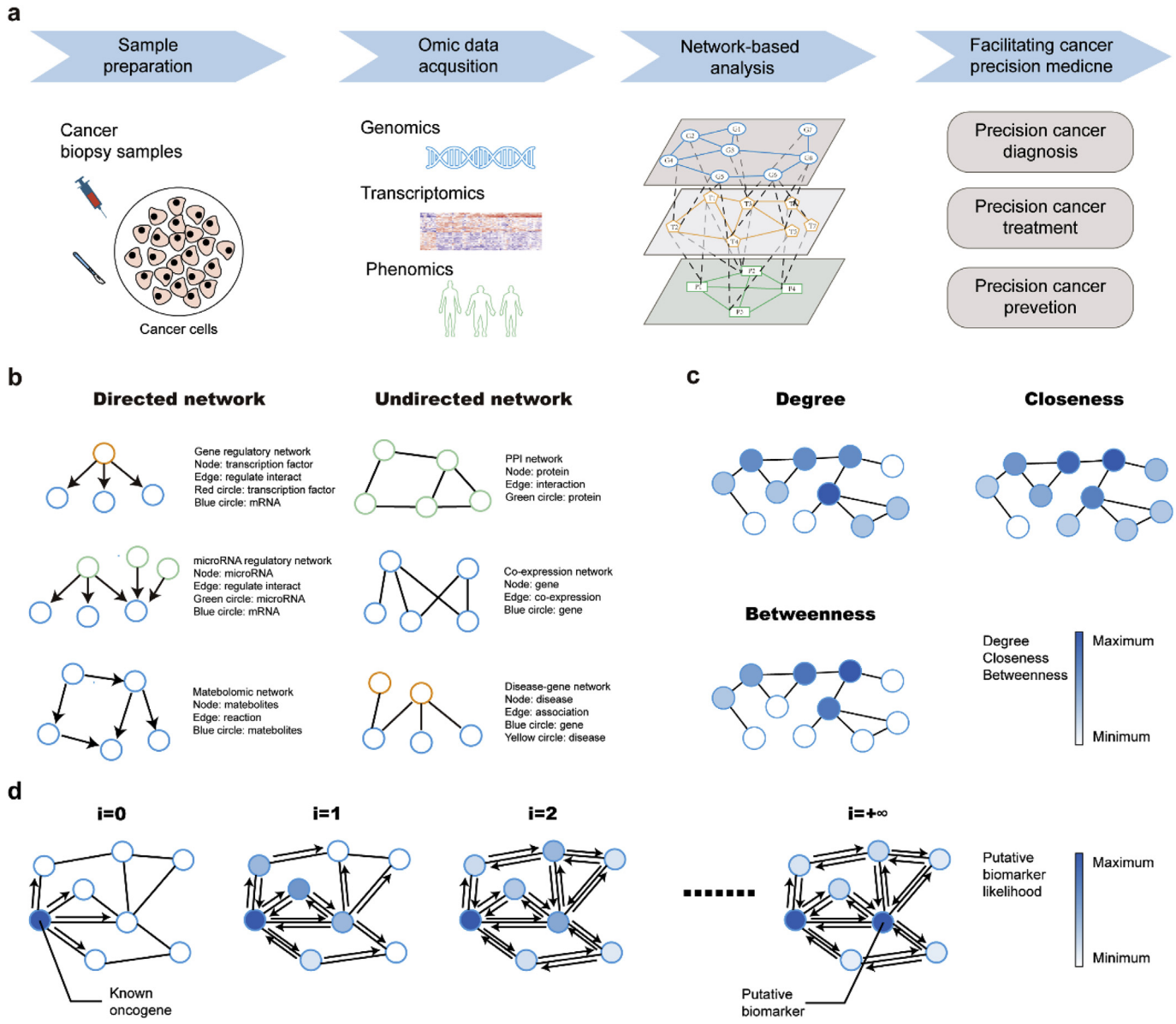

Fig. 1. Schematic diagrams of network basics in cancer precision medicine.
a) Typical network-based research procedure in cancer precision medicine.
b) Examples of biological networks widely used in cancer research which can be categorized into directed and undirected networks.
c) Three commonly used network centrality measures illustrated in an undirected example network: degree, closeness, and betweenness.
d) Step-by-step demonstration of network propagation which depicts a process of biomarker identification for cancer diagnosis based on known oncogenes.

of cancer [18], thus could exploit new advances in precision cancer diagnosis, treatment, and prevention (Fig. 1a). Network science is a research field which concentrates on the studies of complex networks, such as social networks, computer networks, and biological networks [19]. By modeling biological entities as nodes and connections between them as edges, network-based methods could focus on the interactions between molecules, pathways, cells, organs, and individuals [20], rather than single building blocks of the complex system, and play a pivot role in addressing fundamental biological questions at different scales [21–24].

Biological relationships are generally modeled in two ways, based on whether the causality is concerned (Fig. 1b). Directed networks, in which edges have associated directions, are often used to depict the causal relationships between two entities. For example, the regulations between miRNAs and their mRNA targets can be represented using a directed network with arrows from miRNAs to mRNAs. On the other hand, undirected networks are regularly adopted when only associations between two entities are captured, such as a co-expression network built on the correlations between expressions of pairs of genes.

Traditionally, these biological relationships are extracted from experimental data under one single condition, such as protein-protein interactions discovered in the yeast two-hybrid system, which makes the network constructed from them “static”. For these static networks, topological methods from graph theory are commonly applied to glean insights into the complex system. Although a few dynamic properties could be deduced from a static network, such as controllability [25] and observability [26], our understanding of its response to internal regulations, environmental perturbations, or clinical treatments, is still limited [15]. With rapidly decreasing costs of high-throughput sequencing and other massively parallel technologies, it has become feasible to investigate biological relationships and their variations across multiple conditions. One class of network-based approaches to utilize such data, denoted as differential network analysis, is to construct static networks for each molecular profile and to identify network

topological changes between every two states [27]. Others use quantitative techniques to analyze the complex dynamic behaviors directly, among which kinetic modeling has drawn accumulating attentions since it could be extended to unexplored conditions and thus be used to reveal the fundamental physical principles of complex systems, such as the dynamical evolution and the emergent behavior [28].

Modern complex network theory has provided comprehensive tools to yield novel insights into tumor pathogenesis and progression. Taking cancer driver identification for example, which could be interpreted as "identification of important nodes" under proper settings [29], various network-based methods from network centrality measures (Fig. 1c) [30] to network propagation (Fig. 1d) [31] could be applied. The degree, defined by the number of edges adjacent to one node, is the most intuitive indication of vital nodes in complex biological networks. The derived widely used concept "hub" plays a critical role in governing biological processes and functions [32], such as liver metastasis of gastric cancer [33]. And due to the incompleteness of known molecular interactions [34] and the scale-free characteristics of biological networks (new nodes and edges tend to link to nodes with large degree) [35], hubs may be found even more crucial as new interactions emerging. However, researches on transcriptional networks indicated that, although transcriptional factors have higher degrees than average, they are not the dominant hubs in the network [36]. Thus, distinct network measures should be used for different biological networks. For example, Zhang et al. [37] used the betweenness centrality, which describes the number of times a node appears in the shortest path of every two other nodes in the network, to assess the importance of miRNAs and proteins within each corresponding layer built on maximal information coefficients, and successfully identified molecules potentially served as early diagnosis biomarkers for breast cancer. On the other hand, inspired by algorithms from diverse fields, network propagation, which could be described by moving indicators from the nodes with initial values (known disease genes) to adjacent nodes with probabilities proportional to the weights of the links (for example, correlations of expressions) and repeating steps until convergence, considers the full network topology as well as node properties and offers the state-of-the-art performance [38].

3. Micro-level network applications in cancer precision medicine

Recently, network approaches have been broadly employed in researches of cancer precision medicine. The predominant application is to reveal novel knowledges related to the tumorigenesis and progression missed by traditional linear methods, ranging from identification of driver genes and mutations [39] and discovery of putative biomarkers [40], to tumor molecular subtyping [41]. In this scenario, networks are often used to infer causalities and to increase the statistical power through vertical aggregation (i.e. across different levels of data from the same cohort) and horizontal aggregation (i.e. combining cohorts from different studies). As for cases confounded with severe heterogeneity where few mutations are shared within the group, efforts using networks to stratify patients have been reported [42]. Finally, as a promising tool for drug development, network pharmacology, could expand current space of druggable targets and provide useful guidance for the development of target cancer therapies, while yet remains to be explored [43,44]. In this part, we focus on the network studies based on the micro-level datasets such as genomics, transcriptomics and epigenomics.

3.1. Network biomarker

Network models have been proven to be useful for prioritizing and identifying disease genes and pathways by integrating orthogonal data types to narrow down the search space [45,46]. Particularly, these networks have been used to identify driver genes and pathways in genome-wide molecular profiles of tumors including single-nucleotide polymorphism [47] and gene expression data [48] in which case that few significant hits were yielded by direct statistical analyses. As the case in NetSig [49], the tumorigenic potential of AKT2 and TFDP2 was found when reanalyzing 242 lung adenocarcinomas patients without mutations and amplifications in established oncogenes by integrating protein interaction networks with data from tumor exomes.

Besides, network methods could also search a set of biological entities related to certain disease traits, namely the disease module [50,51], in which genes or proteins interact with each other closely while may regulate different cellular biological processes [52]. The derived disease module may serve as a new type of biomarker, denoted as network biomarker [53], for prognostic and predictive usage, such as detecting the pre-cancer state [54] and indicating the tipping point of pulmonary metastasis [55]. For instance, in chronic gastritis patients with Cold/Hot Syndrome which are thousand-year-old therapeutic concepts in traditional Chinese medicine (TCM), imbalanced network biomarkers indicating a metabolism-immune dysregulation were identified [56]. This metabolism-immune imbalance, also revealed by a mathematical model [57], may elucidate the mechanisms underlying gastric oncogenesis and link TCM Cold / Hot syndromes to cold / hot tumors (whether the immunologic status of tumor microenvironment is suppressed or activated) [58], thus making this work as a bridge for the gap between the ancient medicine and complex biological systems [59].

Additionally, network modules, elucidating crosstalk between different pathways and/or feedback and feedforward regulatory loops, could be used to glean insights into the biological mechanisms underlying tumorigenesis and progression [60,61]. For example, Singer et al. [62] analyzed single-cell RNA expressions of $CD8^+$ tumor-infiltrating lymphocytes and identified a distinct gene module for T cell dysfunction which is downstream of intracellular metallothioneins that regulate zinc metabolism and can be uncoupled from T cell activation, which provided novel opportunities for targeting dysfunctional T cell states. Rajbhandari et al. [63] identified a 10-protein module, which is centered around a YAP/TAZ-independent TEAD4–MYCN positive feedback loop, as the transcriptional driver of a high-risk neuroblastomas subtype featured by MYNC amplification through regulatory network analysis, and further validated that TEAD4 emerged at the top of such regulatory hierarchy is a highly conserved, mutation-independent tumor vulnerability for this specific subtype.

3.2. Network stratification

An important issue in cancer precision medicine is to stratify tumors into clinically and biologically meaningful subtypes according to the similarities between their molecular profiles [64]. Different approaches based on various data source have been proposed, such as using mRNA expressions to classify patients into groups that will benefit from specific therapies in breast cancer [65]. However, due to the intra- and inter-heterogeneities of tumors, it is challenging to define an entire tumor subtype on a single molecular event. Thus, efforts have been dedicated on searching combinations of genomic driver events or network modules for stratifications [66,67].

Hofree et al. [42] proposed a network-based stratification method integrating molecular networks with mutation profiles to stratify tumors into clinical subtypes by projecting the binary sparse mutation profiles of each patient onto a gene interaction network, spreading the influences over the network to get a smoothed profile for each patient which is neither binary nor sparse, and clustering by similar network regions using regularized non-negative matrix factorization. This network-based method and similar approaches have successfully divided cancer patients into groups related to tumor histology, treatment response or overall survival in gastric [68], kidney [69], endometrial [70], and prostate cancers [71].

3.3. Network target

The traditional approach of drug design and discovery which relies on “one target, one drug” has influenced identification of actionable targets, classification of disease, drug screening as well as in the design of clinical trials [72]. As a promising tool for drug development, network pharmacology allows a paradigm shift from the single-target approach to a network-target strategy [73,74]. Different from the reductionism which isolate drugs or targets from each other, it adopts a network perspective to consider the complex interactions among genes, proteins, metabolites and compounds under the context of a certain disease [75]. Currently, through network modeling, researches could conduct *in silico* analyses of single anti-cancer agents and identify possible synergistic drug combinations, as discussed below.

As a key concept in network pharmacology, "network target" evaluates the variation of the whole network perturbed by one or multiple agents [74]. This global thinking which takes not only direct targets but also off-target effects and their network neighbors into consideration has been proved valuable when repositioning approved drugs [76] and recognize the biomolecules whose mechanisms remain unexplored [77]. As an example, to unveil the consensus of the biological basis of health-strengthening (*Fu-Zheng*) herbs, a representative type of TCM therapy widely used for cancer treatment in China, Zheng et al. [78] analyzed the network target profiles of 1446 compounds out of 22 herbs and found a greater potential of tumor microenvironment regulation and cancer prevention than direct killing the tumor cells which was later supported by data from high-throughput technologies.

Based on network target effect analysis of single agents, efforts have been further put into the prediction of synergistic combinations. By perturbing specific nodes in the drug-target network, Choi et al. [79] predicted and validated that nutlin-3, an MDM2 inhibitor, though has limited effectiveness alone, but would synergize with WIP1 inhibition to trigger cell death in breast cancer. On the other side, this approach could be employed to systematically understand the mechanisms of synergistic combinations established in ancient medicines [80,81], from compatibilities [82] to herb formulas [83]. For example, Guo et al. [84] established a network-based combinatorial CRISPR-Cas9 screening strategy, identified all possible genetic interactions (GIs), including synthetic lethality and synergistic promotion, within and between three functional modules associated with colorectal tumorigenesis, and demonstrated the potential of these GIs to serve as synergistic target combinations for Liu-Wei-Di-Huang, a classical TCM prescription, through a network-target analysis and further experimental validations. Thus, the network target approach is now accelerating a network-based precision TCM in cancer prevention and treatment.

4. Systematically-integrated network applications in cancer precision medicine

As a convenient computational framework, network-based models have been successfully applied to identify distinct patterns from noisy and incomplete observations by integrating multiple types of micro-level data [85–87]. However, in order to stratify cancers into subtypes according to their underlying biological mechanisms and to develop effective tumor targeted therapies, cancer precision medicine requires the understanding of not only the genetics, but also the phenotypes and the precise relationship between them [88,89]. Furthermore, with easily accessible measures and novel machine-learning methods, phenotypes enable us to trace causal links between genotypes and environmental factors, which may benefit the realization of the potential of cancer prevention [90]. As pioneers considering genotypes and phenotypes as a whole system, network-based systematic integration methods could be categorized into two types (Fig. 2), namely forward systematic integration and reversed systematic integration, borrowing concepts from molecular genetics, as discussed below.

4.1. Forward systematic integration

Starting with an incomplete molecular network of a certain phenotype of interest built on existing knowledges, forward systematic integration uses network-based methods to discover unrevealed links, such as novel disease-gene associations [91], aberrant enhancer-gene regulation [92], or therapeutic drug-phenotype relationships [93]. Often, the bottleneck of this group of methods is the low coverage of available interaction maps of this phenotype [94]. To address such challenge, methods could integrate interactions unrelated to human phenotypes (for example, protein-protein interactions verified in *in vitro* experiments) and/or borrow information from other phenotypes by assuming that similar phenotypes tend to share same underlying mechanisms which is strongly supported by modern genetics [95]. For example, beginning with 23 known ataxia-associated genes, Lim et al. [96] used yeast two-hybrid assays to map their interactions with other human proteins and found puratrophin 1 linked to ataxia through a network module analysis [97]. The “forward” here indicates that the information flows from macro-levels (such as social, phenotypic and microbiome ones) to micro-levels (such as genomic, epigenomic and transcriptional ones) in network models.

Variants of this methodology have been developed and applied to different types of cancers [33,98–100]. Su et al. [101] used a genome-wide disease gene predictor [102] which correlated a phenotype network and a protein-protein interaction network to reveal that two distinct disease modules exist and have crosstalk through the interactions between IL-1β/IRAK1 and Gankyrin in hepatocarcinogenesis. Similarly, López-Cortés et al. [103] used a network-based algorithm ranking disease genes for user-supplied phenotype terms [104] to identify genes related to the early-stage breast cancer which has been validated by other computational strategies and *in vitro* functional experiments.

Recently, advances in comprehensive characterization of cancer tissues, such as single-cell mRNA sequencing, have revolutionized our ability to acquire detailed data at both macro-levels and micro-levels. Utilizing forward systematic integration, this would further improve our understanding of tumorigenesis and progression, and exploit new opportunities in cancer diagnosis, prevention, and treatment. For example, from patients with gastric premalignant lesions and early gastric cancer (EGC), Zhang et al. [105] generated a single-cell atlas and integrated it with high-risk gene profiles predicted to be associated with the phenotypes specific in EGC. This work yielded OR51E1 as a novel marker for early-malignant enteroendocrine cells, and identified a panel of EGC-specific signature from the network which has clinical implications for the precise diagnosis of EGC. In summary, forward systematic methods help us shape an integrated understanding of the interactions among the molecules, the environment and the pathophenome, thus linking pathological biology to clinical research and drug discovery, aiding our investigation of tumor mechanisms and, eventually, the development of rational precision cancer therapies [106].

4.2. Reversed systematic integration

On the contrary, reversed systematic methods employ knowledges at the micro level, such as the cell proliferation rate of a specific cell type, and integrate them into a network-based mathematical model. Through numerical simulations, these methods could contribute to the elucidation of complex mechanisms underlying the phenotype of interest and make useful quantificational predictions that can be validated, especially in the field of precision cancer prevention [107], by combining with animal models [108] and experiences derived from successful cases [109].

The power of reversed systematic methods lies in its ability to depict the complex dynamic tumor microenvironment which involves multiple cell types interacting among each other in diverse ways [110,111], to

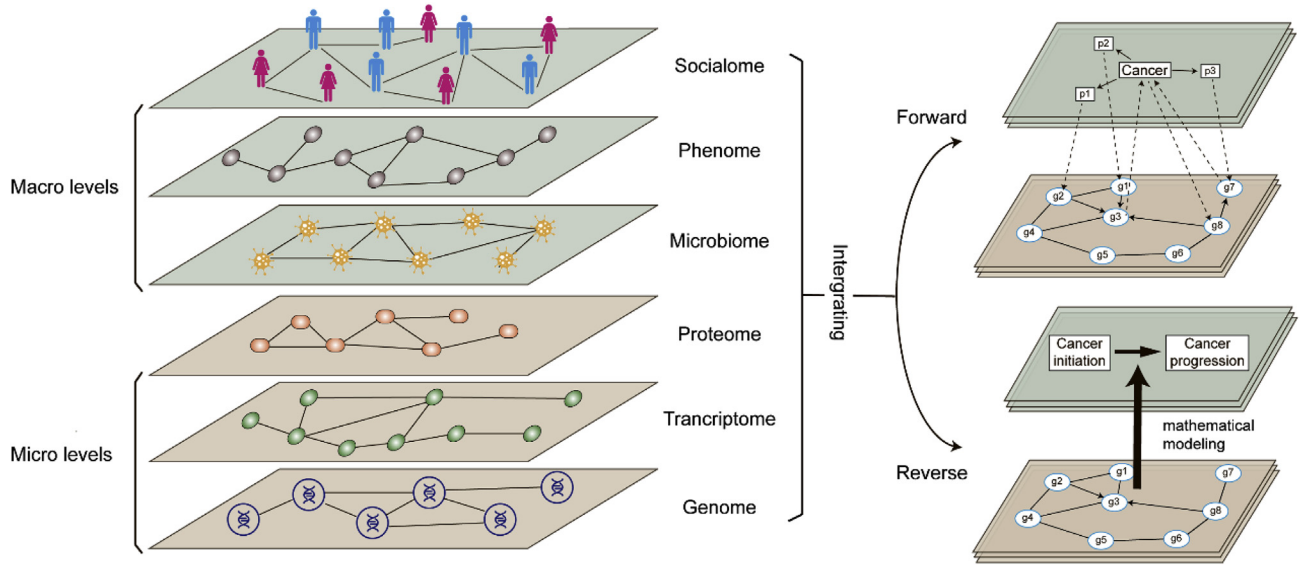

Fig. 2. Schematic diagram for network-based systematic integration.
Network models serve as a convenient computation framework to systematically integrate data across macro- and micro-levels. Forward systematic methods integrate data of a certain phenotype and similar phenotypes to reveal the underlying molecular mechanisms, while reversed approaches build mathematical models at micro-levels to elucidate and predict characterizations in macro levels.

explain the mechanisms underlying the dynamical evolution and the emergent behavior [112,113], and thus to reveal previously unknown principles which have been missed by qualitative approaches owing to the temporal heterogeneous of tumor [114]. For example, Guo et al. [57] proposed a model incorporating the crosstalk between the inflammation environment and cellular functions at different scales ranging from DNA damage response (at intra-cellular level and within minutes to hours) and cell cycling (at individual cell level and within approximately 20 h for colonic epithelial cells), to the prolonged progression towards inflammation-induced cancer (for a cell population mimicking the tissue and within decades) and revealed competing oncogenic and onco-protective roles for inflammation. Although remarkable progress has been made, network-based reversed systematic methods could only make limited contributions to certain phenotypes, such as metastases, mostly owing to the lack of detailed data which impedes the model to obtain accurate parameters [107], where intensive collaborations between computational biologists and experimental as well as clinical researchers is needed.

5. Future perspectives

While cancer precision medicine keeps making breakthroughs, it has become evident that there are limits to single-targeting practices, such as benefiting a relatively small proportion of the patients who received assays [115]. There is a pressing need for establishing new paradigms to overcome spatial and temporal heterogeneities in the tumor microenvironment and to develop efficient targeted cancer therapies [116,117].

Network-based strategies hold great promise in supporting such transition from the “single-gene-based” paradigm to a “network-based” paradigm for cancer precision medicine research. With generality and representation simplicity, network-based methods have been repeatedly proven to be powerful models and tools in cancer researches for investigating and integrating data of different types from phenomics to genomics to reveal biological knowledges that could not have been discovered from a reductionistic perspective [118].

In this review, diverse applications of network science to cancer precision medicine are discussed, including identification of disease genes and modules, stratification of tumors into informative subtypes with clinically relevant differences, development of multiple nodes targeting drugs or combinations, and systematic integration of data across macro- and micro-levels. Although there are numerous challenges yet to overcome, the era of network-based cancer precision medicine is emerging.

Conflicts of interest

There are no conflicts of interest to disclose.

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