Architecture of Signature miRNA Regulatory Networks in Cancer Chemoprevention

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Abstract With new high-throughput technologies and superior computational power available for application to current pharmacology research, biomarker discovery has probably entered its most exciting phase to date, especially with the concurrent advent of systems network biology for "big data." Study of recurrent network motifs in network architecture can inform us better about regulatory pathways in the cellular milieu, more so in complex disease states like cancer. In this review, we focus on the architecture of miRNA networks with emphasis on chemoresistance networks in response to chemotherapeutic drugs, chemoprevention networks modulated by dietary phytochemicals, and novel bifunctional networks comprised of bifunctional miRNAs that operate in both chemoresistance and chemoprevention. Since miRNA cancer networks are very complex, the regulatory architecture in chemoresistance and/or chemoprevention may likely include added dimensions of modulation by epigenetic miRNAs and lncRNAs, which may explain, at least in part, the bifunctionality associated with signature miRNA nodes in these networks in addition to temporal dynamics, spatial localization, and stress conditions in the dynamic networks representing the complex cellular milieu. Collectively, by a perusal of our chemoresistance, chemoprevention, and bifunctional networks, we can gain deeper insights into the architecture of signature miRNA regulatory networks in cancer that will serve as the basis for future dynamic network studies and facilitate the discovery of novel miRNA/target biomarkers for preventive and/or therapeutic intervention in cancer.

Keywords Big data · Biomarker · Bifunctional network · Cancer · Chemoprevention · Chemoresistance · miRNA · miRNA signature · Network · Network motif · Systems biology

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Abbreviations

AITC	Allyl isothiocyanate
ATRA	All trans retinoic acid
CoMi	Context-specific miRNA regulation
DATS	Diallyl trisulfide
DIM	3,3′-Diindolyl methane
EGCG	Epigallocatechin-3-gallate
FBL	Feedback loops
FFL	Feed-forward loops
HRPC	Hormone refractory prostate cancers
I3C	Indole-3-carbinol
Jak/STAT	Janus kinase/Signal transducer and activator of transcription
lncRNA	Long noncoding RNA
MDRL	Mitochondrial dynamic related lncRNA
mirDREM	MIRna Dynamic Regulatory Events Miner
miRNA	MicroRNA
NFATC3	Nuclear factor of activated T cell isoform c3
PEITC	Phenethyl isothiocyanate
SCC	Squamous cell carcinoma
TP	Tumor protein
TRPC5	Transient receptor potential channel C5

Introduction

Despite substantial progress in understanding the cancer signaling network, effective therapies remain scarce due to insufficient disruption of oncogenic pathways, chemoresistance, and drug-induced toxicity [1••]. Defects in the DNA damage response and deregulation of microRNAs (miRNAs) are important hallmarks of human cancer; hence, a full understanding of the mechanisms underlying the connection between miRNAs and DNA damage response and DNA repair pathways will positively impact our knowledge on human tumor biology and on different responses to distinct drugs [2]. By definition, miRNAs are small noncoding endogenous regulatory RNAs that fine tune gene expression in a wide range of biological processes and diseases, and exert their function by targeting mRNAs to trigger their degradation or inhibit protein translation [3•]. According to current estimates, most human genes are harboring miRNAs and/or are regulated by them; thus, miRNAs can form complex regulatory networks by themselves, but because their expression is often tightly coordinated with gene expression, they form an intertwined regulatory network with many possible interactions among gene and miRNA regulatory pathways [4]. Indeed, identifying master regulators of biological processes and mapping their downstream gene networks are key challenges in systems biology that remain to be overcome [5]. Although initially seen as a very promising source of breakthroughs in cancer management, there has been little translation of miRNA science from the bench to the bedside, thus underscoring the need to highlight the potential role of miRNAs in cancer prevention, viz., their use as biomarkers and as targets for chemoprevention [6]. Given their significance in modulating gene expression, miRNA research can provide insight into the pleiotropic biological effects that chemopreventive agents often display and a deeper understanding of their mechanism(s) of action to inhibit carcinogenesis [7]. In this review, we focus on the architecture of miRNA networks with emphasis on three kinds of important networks in cancer, viz., chemoresistance networks in response to chemotherapeutic drugs, chemoprevention networks modulated by dietary phytochemicals, and novel bifunctional networks comprised of bifunctional miRNAs that operate in both chemoresistance and chemoprevention.

Systems Biology of microRNA Cancer Networks

The biological sciences are in a state of rapid development, driven largely by the new technologies that have developed as byproducts of the Human Genome Project; thus, the true revolution inspired by genomics is probably changing what was exclusively a laboratory science into an information science [8]. Rather than focusing exclusively on single drug targets, systems pharmacology examines the holistic response of a phenotype-dependent pathway or pathways to drug perturbation [9]. "Top–down" systems biology identifies molecular interaction networks on the basis of correlated molecular behavior observed in genome-wide "omics" studies, whereas "bottom–up" systems biology examines the mechanisms through which functional properties arise in the interactions of known components [10]. Importantly, data integration efforts can be achieved through the conversion of data from the various datasets of recent large-scale projects into single-node-type networks, gene-set libraries, or multipartite graphs resulting in a lean "big data" integration strategy that could bring us closer toward the goal of realizing personalized medicine [11].

miRNA Network Biology and Cancer Biomarker Discovery

We have recently reported [12••] on our use of systems pharmacology for elucidation of differential signaling regulatory networks governing hormone refractory prostate cancers (HRPC) and identification of putative "target hubs" in the architecture of these gene networks. In addition, we have constructed [13] transcription factor networks to elucidate potential relationships between NRF2 (NFE2L2) and NFκB1 in the etiopathogenesis of inflammation and cancer. Similarly, it is known that the miRNA network is linked at several and unexpected levels with cancer-related signaling pathways; thus, our understanding of the role(s) and regulation of the miRNA network has been extended to include classical cell signaling, i.e., the miRNA network complements cell signaling in cancer [14]. Recently, high-throughput sequencing coupled with network analysis [15] was used to identify cancer-specific miRNA signatures and potentially useful biomarkers in colorectal cancer. Zhang et al. [16] reconstructed the human miRNA–mRNA interaction network exhibiting scale-free features and designed a novel cancer miRNA biomarker prediction framework applied to prostate cancer study that could also be extended to other cancers. Further, Zhu et al. [17] used network biology for predictive marker discovery using context-specific miRNA regulation (CoMi) patterns to represent a distinctive feature of the miRNA regulatory network in the transcriptome. Indeed, the utility of miRNAs as prognostic biomarkers and possible druggable target(s) for circumventing multidrug resistance in cancer chemotherapy [18] is now being greatly appreciated.

Architecture of miRNA Networks in Cancer

Emerging models supporting an miRNA-modulated systems-level or network-wide regulation of gene expression are exciting and will yield deep insight into the regulatory architecture of biology; however, because of the technical challenges facing the network-based study of miRNAs,

many gaps remain in our understanding [19]. Network motifs are subgraphs that are statistically overrepresented within networks [20]; hence, recurring network motifs may have important gene regulatory role(s). Interestingly, transcription factors and miRNAs can jointly regulate target gene expression in the forms of feed-forward loops (FFLs) or feedback loops (FBLs), which serve as important motifs in gene regulatory networks [21] and play critical roles in multiple biological processes and different diseases. The proteins encoded by the genes targeted by miRNAs may act as key components of cellular networks; thus, the use of biological molecular network information for the purposes of elucidating the role of miRNAs in molecular disease mechanisms is a key objective in systems biomedicine [3•]. Further, because miRNAs can modulate epigenetic architecture and can be regulated by epigenetic alteration, they can reasonably play an important role(s) in mediating the crosstalk between epigenetic regulators; thus, study of the epigenetic-miRNA regulatory pathway is a promising avenue for the design of innovative strategies in the fight against human cancer [22].

microRNAs and Chemoresistance Networks

One of the most important factors limiting the effectiveness of chemotherapy is the primary and secondary resistance of cancer cells; thus, understanding the genetic factors and mechanisms that contribute to the lack of or low sensitivity of tumor tissue to cytostatics is a key element in the currently developing trend of personalized medicine [23]. There is known to be great heterogeneity in tumors with chemoresistance [24], which makes the disease far more difficult to treat using conventional chemotherapy acting on limited known targets. Indeed, drug resistance is a complex multistep process resulting from deregulated expression of many molecules, including tumor suppressor genes, oncogenes, and miRNAs [25]. A growing body of evidence suggests that miRNA polymorphisms are associated with drug metabolism and chemoresistance and that differentially expressed miRNAs play critical roles in the prediction of sensitivity to chemotherapeutic agents [26]. Experimental evidence demonstrates that dysregulation of specific miRNAs leads to drug resistance in different cancers, and correction of these miRNAs using miRNA mimics or antagomirs can normalize the gene regulatory network and signaling pathways and sensitize cancer cells to chemotherapy [1••]. Thus, current evidence strongly reinforces the case for a better understanding of drug resistance-related miRNAs that may eventually lead to optimized therapeutic strategies for cancer patients [25].

Fig. 1 Architecture of chemoresistance, chemoprevention, and ▶ bifunctional cancer networks showing: **a** putative canonical interactions between miRNAs involved in chemoresistance, **b** epistemologic interactions between chemoresistance miRNAs and targets, **c** putative canonical interactions between miRNAs involved in chemoprevention, **d** epistemologic interactions between chemoprevention miRNAs and targets, **e** putative canonical interactions between miRNAs involved in cancer bifunctionality, and **f** epistemologic interactions between bifunctional cancer miRNAs and targets. Putative canonical miRNA interactions were constructed using Cytoscape 3.1.1 [125, 126], whereas epistemologic miRNA–target interactions were delineated by Ingenuity Pathway Analysis (IPA, http://www.ingenuity.com). The bifunctional cancer network E comprised a subset of miRNAs that were common to both chemoresistance and chemoprevention networks **a** and **c**, respectively

miRNAs Involved in Chemoresistance Against Chemotherapeutic Drugs

In our previous report [27••] on emerging role(s) for miRNA cancer signatures, we had succinctly tabulated various chemotherapeutics along with up- or downregulated miRNAs involved in resistance against them. Building on this, we reviewed 24 chemotherapeutic agents including 5-fluorouracil [28–33], bortezomib [34], camptothecin [35], cetuximab [36, 37], cisplatin [38, 39], dasatinib [40], daunorubicin [41], docetaxel [39, 42, 43], doxorubicin [44–47], erlotinib [48], everolimus [49], fludarabine [50, 51], fulvestrant [52], gefitinib [53–55], gemcitabine [56–58], imatinib [59], lapatinib [55], methotrexate [60, 61], paclitaxel [38, 62], sorafenib [63], sunitinib [64], tamoxifen [65], temozolomide [66–68], and trastuzumab [69], and miRNAs involved in drug resistance to these agents. These miRNAs are included in Fig. 1a that depicts the architecture of our proposed canonical chemoresistance network showing putative interactions between 55 miRNA nodes or vertices involved in chemoresistance and 2970 undirected edges facilitating these interactions. Further, we queried these miRNAs for interactions with targets to construct an epistemologic chemoresistance network showing "arcs," i.e., directed edges, connecting miRNA nodes of the network (Fig. 1b).

Architecture of Chemoresistant miRNA Networks

miRNAs are involved in many regulatory pathways some of which are complex networks enriched in regulatory motifs like positive or negative FBLs or coherent and incoherent FFLs [70]. A methylation-based regulatory network for miR-320a in chemoresistant breast cancer through targeting of transient receptor potential channel C5 (TRPC5) and nuclear factor of activated T cells isoform c3 (NFATC3) has recently been reported [71]. The existence of FBLs between E2F1 and miRNAs have been reported [72] resulting in a complex regulatory network. Vera et al. [73] performed
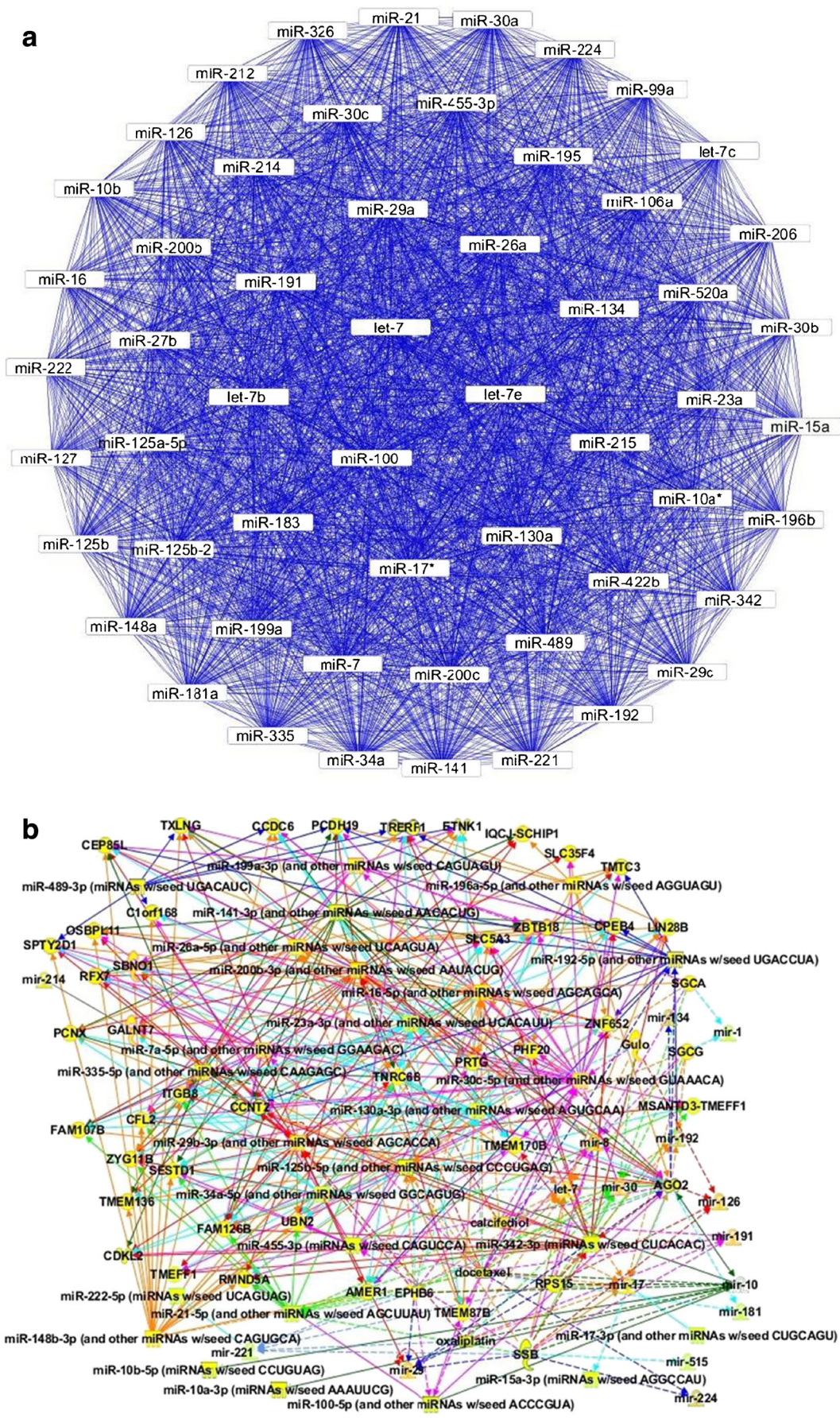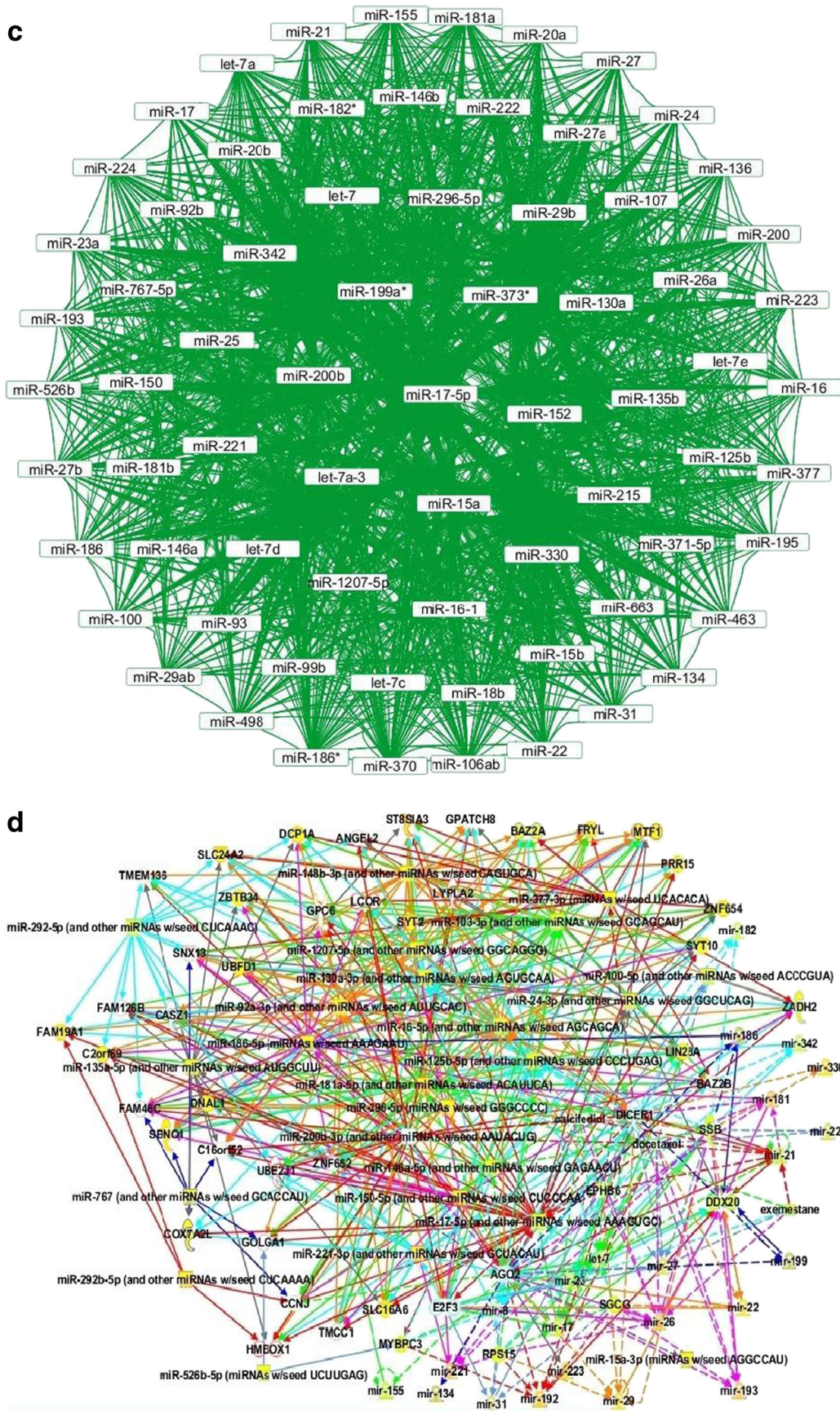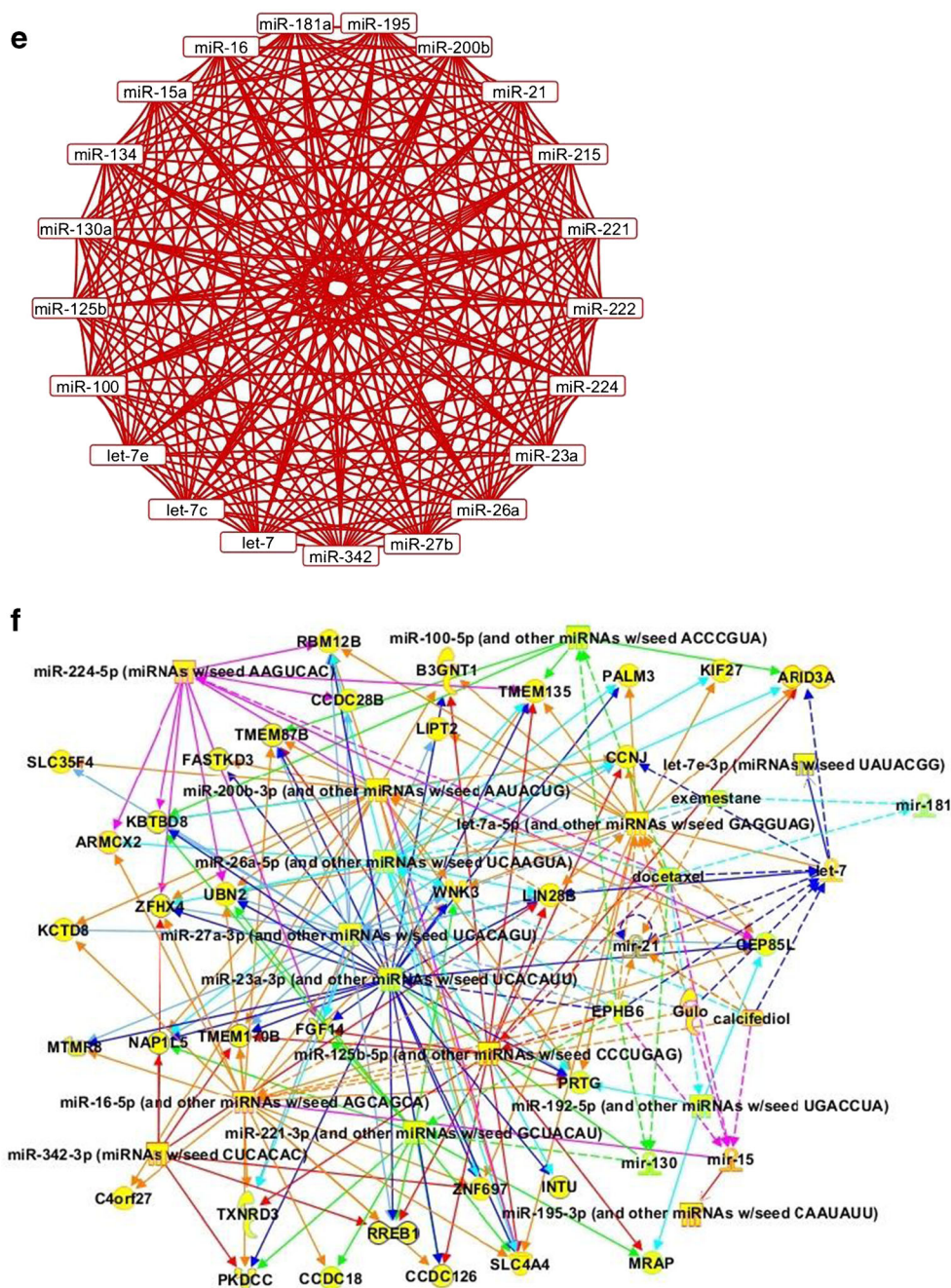
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kinetic-modeling-based simulations to demonstrate that conventional genotoxic drug treatment favors selection of chemoresistant cells in genetically heterogeneous tumors, in a manner requiring dysregulation of incoherent FFLs that involve E2F1, p73/DNp73, and miR-205. Kopp et al. [74] showed that miR-200c sensitizes breast cancer cells to doxorubicin treatment by decreasing expression of receptor tyrosine kinase TrkB and the transcriptional repressor Bmi1, whereas loss of miR-200c resulted in acquired chemoresistance to doxorubicin. Ratovitski [75] showed recently that cisplatin exposure of squamous cell carcinoma

SCC-11 cells led to upregulation of miR-297, miR-92b-3p, and miR-485-5p through a phosphorylated ΔNp63α-dependent mechanism and that the tumor protein (TP) p63/miRNA functional network may play a key role in supporting the response of SCC to chemotherapy. Lecca [76] has described Bayesian methods of biological network inference for reverse engineering cancer chemoresistance mechanisms. Indeed, network-based therapy that affects network flexibility, including rewiring of network structures and focusing on "target hub" molecules in these networks, could minimize the occurrence of side effects and be a promising strategy for

enhancing the therapeutic efficacy of cancer treatments in chemoresistance and radioresistance [77]. Based on our chemoresistance network in Fig. 1b, several miRNA nodes with high "degree," i.e., "number of interactions" were visible including miR-148b-3p, miR-21-5p, miR-10, miR-455-3p, miR-342-3p, miR-34a-5p, miR-125b-5p, miR-30, let-7, miR-29b-3p, miR-8, miR-130a-3p, miR-30c-5p, miR-335-5p, miR-7a-5p, miR-23a-3p, miR-16-5p, miR-200b-3p, miR-192-5p, miR-26a-5p, miR-141-3p, miR-489-3p, miR-199a-3p, among others. Further, autoregulation was observed for miR-29 and miR-29b-3p; also, let-7 and miR-30 exhibited highest "in-degree," i.e., arrows pointing towards these nodes in the directional miRNA network, whereas most other miRNA nodes exhibited higher "out-degree," i.e., arrows pointing away from these nodes in Fig. 1b. In addition, several targets of the miRNAs with high "degree" were observed in the network in Fig. 1b including ZBTB18, CCNT2, AGO2, TRERF1, ETNK1, PCDH19, CCDC6, TXLNG, CEP85L, SLC5A3, TNRC6B, EPHB6, LIN28B, among others, that may be important in mediating chemoresistance via miRNAs.

microRNAs and Anti-cancer Chemoprevention Networks

Chemoprevention is a pharmacological approach to intervention in order to arrest or reverse the process of carcinogenesis [78]. We have noted earlier [79•] that mammalian cells, including human cells, respond to dietary phytochemicals by "nonclassical receptor sensing" mechanisms of electrophilic chemical-stress typified by "thiol-modulated" cellular signaling events primarily leading to the gene expression of pharmacologically beneficial effects, but sometimes unwanted cytotoxicity also. Interestingly, specific targeting of miRNAs by natural agents could open newer avenues for complete eradication of tumors by killing drug-resistant cells to improve survival outcomes in patients diagnosed with malignancies [80••]. Indeed, as previously observed [81] by us, although the precise mechanism underlying the control of miRNA expression in chemoprevention is not well understood currently, epigenetic changes could play a major role.

miRNAs Modulated by Anti-cancer Chemopreventive Agents

A summary of miRNAs modulated by several anti-cancer chemopreventive agents has been furnished by us earlier [27••]. Building on this, we reviewed the literature for 17 chemopreventive agents (and miRNAs) including all trans retinoic acid (ATRA) [82, 83], allyl isothiocyanate (AITC) [84], boswellic acid [85], calcitriol [86–88], curcumin [89–94], diallyl trisulfide (DATS) [95], 3,3′-diindolylmethane (DIM) [96, 97], ellagitannin [98], (−) epigallocatechin-3-

gallate (EGCG) [99–101], genistein [96, 97, 102], green tea polyphenon-60 [103], indole-3-carbinol (I3C) [104], lycopene [105••, 106], phenethyl isothiocyanate (PEITC) [107], quercetin [108], resveratrol [109, 110], and sulforaphane [111]. These miRNAs modulated by chemopreventive agents are included in Fig. 1c that depicts the architecture of our proposed canonical chemoprevention network showing putative interactions between 71 miRNA nodes or vertices involved in eliciting the protective chemopreventive effects of these natural or synthetic dietary factors and 4969 undirected edges facilitating these interactions. Further, we queried these miRNAs for interactions with targets to construct an epistemologic chemoprevention network showing "arcs" connecting miRNA nodes of the network (Fig. 1d).

Architecture of Chemopreventive miRNA Networks

Recently, Sehgal and Ram [112] mapped the upstream and downstream connectivity within the JNK network to reveal an enrichment of bi-fan and FFL motifs formed immediately upstream and downstream of JNK in addition to negative FBL motifs that exist through transcriptional activation of phosphatases that target the JNK pathway. Shah et al. [113] demonstrated in Sprague–Dawley rats that diet and carcinogen exposure modulated a number of miRNAs (miR-16, miR-19b, miR-21, miR26b, miR27b, miR-93, and miR-203) linked to canonical oncogenic signaling pathways. Recently, Song et al. [114] identified a key miRNA regulatory network including miR-200b, miR-200c, and miR-125b that defines the mesenchymal gastric cancer subtype significantly associated with poor overall survival in gastric cancer. Overall, there is very limited information available in the literature on miRNA networks in chemoprevention as the importance of applying network analysis to miRNA chemoprevention research is in its infancy and only beginning to be recognized. Based on our chemoprevention network in Fig. 1d, several miRNA nodes with high "degree" were visible including miR-148b-3p, miR-377-3p, miR-103-3p, miR-292-5p, miR-1207-5p, miR-130a-3p, miR-92a-3p, miR-16-5p, miR-186-5p, miR-125b-5p, miR-135a-5p, miR-181a-5p, miR-296-5p, miR-200b-3p, miR-21, miR-146a-5p, miR-150-5p, miR-17-5p, miR-221-3p, miR-let-7, miR-17, miR-26, miR-192, miR-29, miR-193, among others. Further, autoregulation was observed for miR-21, miR-155, and miR-29; also, let-7, miR-17, and miR-26 exhibited highest "in-degree," whereas most other miRNA nodes exhibited higher "out-degree" in Fig. 1b. Moreover, miR-31, miR-192, miR-29, and miR-193 showed only "in-degree" interactions, whereas miR-17-5p, miR-292-5p, and miR-200b-3p showed only "out-degree" interactions. In addition, several targets of the miRNAs with high "degree" were observed in the network 1d including LCOR, BAZ2A, GPATCH8, FRYL, MTF1, DCP1A, GPC6, ZBTB34, FAM19A1, FAM126B, FAM46C, DICER1, EPHB6,

DDX20, AGO2, E2F3, SLC16A6, CCNJ, TMCC1, HMBOX1, GOLGA1, SBNO1, LIN28A, among others, which may be important in conferring or aiding chemoprotection via miRNA-mediated mechanisms apart from other role(s) in the cellular milieu.

microRNAs and Bifunctional Cancer Networks

To overcome the limitations of a static protein–protein interaction network, Luo and Kuang [115] have recently proposed a new method to predict essential proteins by integrating dynamic local average connectivity and in-degree of proteins in complexes. Extending network dynamics to miRNA networks, Xue et al. [116] showed recently that negative feedback provided by miR-21 stimulates the propensity of oscillations in NFκB and IL-6 activity, while negative feedback provided by miR-146 dampens the oscillations of NFκB and IL-6, suggesting that variations in the relative strength of the two feedbacks may provide for altered response dynamics to the same stimulus, thus revealing a novel regulatory module of two miRNA-mediated negative feedback loops that allow for the fine tuning of the dynamics of key mediators in inflammation. Schulz et al. [117] developed the MIRna Dynamic Regulatory Events Miner (mirDREM), a probabilistic modeling method that uses input–output hidden Markov models to reconstruct dynamic regulatory networks that explain how temporal gene expression is jointly regulated by miRNAs and transcription factors using postnatal lung development in mice for measurements. Guo et al. [118] noted that miRNA variants (termed isomiRs) are potential functional molecules that may affect miRNA stability or target selection, and multiple isomiR products and miRNA maturation processes provide opportunities to perform versatile roles in the regulatory network, which further enriches and complicates the regulation of biological processes. Collectively, it follows that the cancer cellular milieu is a dynamic environment, and it is probable that same miRNAs may perform different, perhaps opposing, functions at different time points or in different stress conditions, which may explain, at least in part, the bifunctional role of the miRNAs, i.e., both chemoresistant and chemopreventive roles, as depicted in Fig. 1e.

Chemoresistant and Chemopreventive Bifunctional miRNAs

Using a simple first-principles approach, we analyzed our networks in Fig. 1a and c to fish out 21 common miRNAs that were present in both chemoresistance and chemopreventive networks, respectively. We then constructed our bifunctional miRNA cancer network Fig. 1e that comprised this common subset of miRNAs that may potentially exert dual functions in both chemoresistance and chemoprevention

probably depending on the cellular milieu, temporal status, or stress conditions. These 21 bifunctional miRNAs included let-7, let-7c, let-7e, miR-100, miR-125b, miR-130a, miR-134, miR-15a, miR-16, miR-181a, miR-195, miR-200b, miR-21, miR-215, miR-221, miR-222, miR-224, miR-23a, miR-26a, miR-27b, and miR-342. Figure 1e depicts the architecture of our proposed canonical bifunctional network showing putative interactions between 21 miRNA nodes or vertices involved in both chemoresistance and chemoprevention and 419 undirected edges facilitating these interactions. Further, we queried these miRNAs for interactions with targets to construct an epistemologic bifunctional network showing "arcs" connecting miRNA nodes of the network (Fig. 1f).

Architecture of Bifunctional miRNA Cancer Networks

Based on our bifunctional network in Fig. 1f, few miRNA nodes with high "degree" were visible, including miR-224-5p, miR-100-5p, miR-200b-3p, miR-26a-5p, let-7a-5p, let-7, miR-27a-3p, miR-23a-3p, miR-125b-5p, miR-16-5p, miR-221-3p, miR-342-3p, among others. Further, autoregulation was observed for miR-21, which was found to be modulated by a large number of chemotherapeutic drugs and chemopreventive agents; also, let-7 exhibited highest "in-degree" among nodes, whereas miR-23a-3p, miR-27a-3p, and miR-26a-5p exhibited highest "out-degree" among nodes in the network in Fig. 1f. In addition, several targets of the miRNAs with high "degree" were observed in the network in Fig. 1f including SLC4A4, PRTG, TMEM170B, FGF14, EPHB6, CEP85L, UBN2, ZFHX4, WNK3, LIN28B, KBTBD8, CCNJ, TMEM87B, TMEM135, B3GNT1, ARID3A, RBM12B, among others, which may be important in both chemoresistance and chemoprotection functions under appropriate spatial and temporal conditions.

Conclusions

With new high-throughput technologies and superior computational power available for application to current pharmacology research, biomarker discovery has probably entered its most exciting phase to date, especially with the concurrent advent of systems network biology for "big data." Study of recurrent network motifs in network architecture can inform us better about regulatory pathways in the cellular milieu, more so in complex disease states like cancer with associated co-morbidities and mortality rates. Recently, Di Carlo et al. [119] described a high-level inter-pathway regulatory motif in complex networks called "pathway protection loop" in which miRNAs play a crucial role in the successful behavior and activation of a pathway resulting in new approaches in the identification of therapeutic targets because it could unveil

novel paths to "activate" or "silence" a target pathway. Indeed, network biology will change the way we look at cellular systems in cancer, and the intrinsic role(s) played by miRNAs will need to be evaluated with a deeper understanding of network dynamics that may confer multiple, sometimes contradictory, roles on signature miRNAs due to spatial and temporal constraints and/or stress conditions. Nazarov et al. [120] investigated simultaneously the transcriptional changes of miRNA and mRNA expression levels using dynamic time series microarray data after activation of the Janus kinase/ signal transducer and activator of transcription (Jak/STAT) pathway by interferon-γ stimulation of melanoma cells, and revealed network motifs in the form of FFLs involving transcriptional regulators, mRNAs and miRNAs. Even in other disease states such as HIV, a phased pattern of miRNA expression was evident by next-generation sequencing, and many miRNAs that were initially suppressed were later overexpressed at the height of infection, providing unique signatures of HIV infection [121]. Hwang et al. [122] analyzed regulatory network dynamics in mouse retina to reveal a natural turning point at which the regulatory network of miRNAs, transcription factors, and protein-coding genes undergoes drastic topological changes, thus demonstrating that adding a dynamic dimension to network analysis can provide new insights into retinal development and suggesting that the same approach would likely be useful for the analysis of other developing tissues. Collectively, it is clear that to avoid the limitations of knowledge from static networks, it is important to invest our time and energies in dynamic networks in cancer chemoresistance and chemoprevention in order to make the best informed choice for preventive/therapeutic intervention in cancer. Further, although epigenetic modifications, such as DNA methylation or histone acetylation, have been demonstrated to affect miRNA expression, and to be potentially responsible for the aberrant miRNA regulation observed in cancer, the other side of the coin is represented by the capacity of epi-microRNAs to control the epigenetic machinery directly targeting its enzymatic components [123]. Interestingly, Wang et al. [124] reported that a long noncoding RNA (lncRNA), named mitochondrial dynamic-related lncRNA (MDRL), affects the processing of miR-484 primary transcript in nucleus and regulates the mitochondrial network by targeting miR-361 and miR-484. On the same note, it is certain that miRNA cancer networks are very complex and the regulatory architecture of cancer chemoresistance and/or chemoprevention networks may likely include added dimensions of modulation by epi-miRNAs and lncRNAs, which may further explain, at least in part, the bifunctionality associated with miRNA nodes in our networks apart from temporal dynamics, spatial localization, and stress conditions. Taken together, by a perusal of our chemoresistance, chemoprevention, and bifunctional networks, we can gain deeper insights into the architecture of miRNA regulatory networks in cancer that will serve as the basis for future dynamic network studies and facilitate the discovery of novel miRNA/target biomarkers for preventive and/or therapeutic intervention in cancer.

Compliance with Ethics Guidelines

Conflict of Interest Sujit Nair and Ah-Ng Tony Kong declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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