Review

Proof of Concept: Network and Systems Biology Approaches Aid in the Discovery of Potent Anticancer Drug Combinations

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Abstract

Cancer therapies that target key molecules have not fulfilled expected promises for most common malignancies. Major challenges include the incomplete understanding and validation of these targets in patients, the multiplicity and complexity of genetic and epigenetic changes in the majority of cancers, and the redundancies and cross-talk found in key signaling pathways. Collectively, the uses of single-pathway targeted approaches are not effective therapies for human malignances. To overcome these barriers, it is important to understand the molecular cross-talk among key signaling pathways and how they may be altered by targeted agents. Innovative approaches are needed, such as understanding the global physiologic environment of target proteins and the effects of modifying them without losing key molecular details. Such strategies will aid the design of novel therapeutics and their combinations against multifaceted diseases, in which efficacious combination therapies will focus on altering multiple pathways rather than single proteins. Integrated network modeling and systems biology have emerged as powerful tools benefiting our understanding of drug mechanisms of action in real time. This review highlights the significance of the network and systems biology–based strategy and presents a proof of concept recently validated in our laboratory using the example of a combination treatment of oxaliplatin and the MDM2 inhibitor MI-219 in genetically complex and incurable pancreatic adenocarcinoma. Mol Cancer Ther; 9(12); 3137–44. ©2010 AACR.

Current Challenges of Targeted Therapy

Although partially successful in some cancers, new adjuvant targeted therapies [p53, NF-κB, epidermal growth factor receptor (EGFR), vascular endothelial growth factor, Src, etc.] for complex malignancies have met with more failure than success (1). The major reason for the low response may be related to an incomplete understanding and lack of validation of the specific molecular targets at the gene level (2). This situation is coupled with complexities of genetic and epigenetic changes in cancer (3), and the redundancies of cross-talk in signaling pathways that, taken together, may explain the observed failure of single-pathway targeted therapies. Moreover, targeted therapy faces complexities of off-targeted effects of many so-called targeted agents (4). Of the 25,000 genes representing the human genome, approximately 1,800 are involved in the etiology of numerous diseases, including cancer (5). Currently available U.S. Food and Drug Administration approved drugs (~1,200 on the market) were designed to target approximately 400 gene products (drugome). Pharmaceutical companies handpicked the protein products of single genes in the drugome to rationally design drugs. However, contrary to the original notion, targeting individual genes in this drugome is not a straightforward task, as the functional product of each gene or (proteome) is under multiple controls, including splice variants and posttranslational modifications, giving rise to more than 40,000 functionally distinct proteins. Previous approaches lacked information on biologically meaningful interconnecting pathways arising from perturbations of single or a set of genes by targeted drugs. This obstacle in our understanding of drug mechanisms of action highlights an urgent need for the use of alternate technologies that would aid in a better understanding of drug mechanisms of action.

The identification of nearly a complete list of genes and gene products in the human body through the human genome project (6) has enabled researchers to draft connectivity maps between proteins (7) and gene expression profiles (8). This mapping helped in the identification of molecules specifically associated with certain pathologic processes, and has benefited the field of drug discovery.
On the basis of these advances in molecular sciences, the initial drug design approaches placed emphasis on target selectivity and enhancement of binding affinities of novel agents to target molecules (9, 10). However, the pathobiology of diseases like cancer is often the result of an incredibly complex combination of molecular events, and despite several success stories, the reductionist approach in drug design and development has led to an unacceptable outcome (11), suggesting that newer approaches must be implemented. Numerous high affinity and specific drugs fail at the last and most costly phase in the clinic, especially in malignancies such as pancreatic adenocarcinoma, arising through the accumulation of multiple genetic alterations and/or mutations in crucial pathways such as p53 (12), DPC4 (12), and k-ras (13, 14). Lack of robust clinical success of such targeted drugs could be attributed to many factors, including inappropriate choice of in vitro cellular models, most importantly due to inadequate knowledge of the crucial interacting pathways. These factors imply that removing targets from their physiologic context and developing drugs solely on the basis of their increasing binding affinity and target selectivity will yield little success. Drug developers are increasingly acknowledging that the next generation pharmacology strategies to fight complex multifaceted disease require targeting multiple pathways rather than inhibiting single proteins.

The significance of using newer methodologies in delineating therapeutic interventions and the networks involved in malignancies, along with the identification of the mechanisms of action, off-target effects of novel agents, and targeted drugs, are being increasingly recognized. However, the lack of proper tools has hindered in-depth understanding of the accumulated knowledge of biological processes to benefit drug discovery and clinical applications (15). In the last few years, novel and high-throughput data acquisition technologies coupled with integrated network modeling and systems biology have emerged as key components of targeted-therapy research (16). These technologies have helped in understanding a drug target protein and/or pathway in its physiologic context with the greatest molecular detail, assisting in the identification of target genes along with clinically relevant drug combinations in a cancer specific manner. Such technologies are crucial for identifying and understanding the mechanisms of potential target candidates in complex diseases, such as pancreatic adenocarcinoma (17). This review presents a strong example of these technologies, and provides confidence in the use of systems-level knowledge of pharmacology derived from extensive genomic information, which can likely increase our understanding in evaluating the efficacy of novel targeted drugs, either alone or in combination treatment. The ultimate goal of such knowledge is directed toward the development of tailored and personalized medicine that is being demanded by the experts in the field, and which is predicted to be the mainstay in the field of cancer treatment in the near future.

Network and Systems Biology: A Powerful New Tool in the Field of Medicine

Systems biology is a science that defines the physical and functional relationships between components responsible for shaping a biological system (18). This technology allows real-time simulation of how biological molecules function in coordination to achieve a particular outcome, consequently providing tremendous power of predicting the drug response in terms of the effect of modulating the function of a given protein or pathway. A network perspective of complex cancers has direct implications in the drug discovery process because it changes the target entity from a single protein to entire molecular pathways and or cellular networks. In recent years, the applicability of these powerful tools has been increasingly recognized in the clinical setting, and researchers are beginning to change the way they think about a complex disease from a gene-centric to a network-centric view (19), although with skepticism. Such an approach identifies a collection of modifiable drug targets (instead of one protein) in their entirety and provides ample and/or optimal points for therapeutic intervention (20, 21). This approach is the key to a successful therapy for disease states that are known to be inherently resistant to drug treatment, because of the maintenance of back-up or alternate survival mechanisms, such as typically observed in pancreatic adenocarcinoma (22). Combining high-throughput bioinformatics, followed by molecular network and systems-level analysis, one can predict genes associated with cancers, biomarkers of response, and novel druggable targets. Such an approach may be applied to case-control cohorts for disease susceptibility or to study individual responses to drugs and their most clinically beneficial combinations. Several inroads have been made in our understanding of cancer development and progression using such network-centric approaches. Examples in which such technology showed benefit include the identification of novel genes associated with increased breast cancer risk, through disease-network analysis of BRCA1 (23). However, the role of these mutational variations in drug response has not been determined in cancers, and most importantly, no such information is available for tumors with complex genetic make-up. Therefore, it is believed that this technology can be effectively used for the management of most cancers in which, at present, specific biomarkers or targets have not been clearly defined. In the following sections, we discuss our recent experience in the use of a systems biology approach in analyzing the synergistic interaction of two anticancer drugs.

Systems Understanding of Drug Action

The goal of applying integrated network modeling and systems biology in medicine is to identify drugs that can be prescribed together, and to discover a combination of targets and modulators to produce synergistic effects. However, prior to applying a systems approach, one
needs to understand the complex and multitiered interactions between various scales of organization starting from a very basic molecular and cellular network, to tissue organization, and finally to organ interaction in the organism. Drug effects on patho-physiology that are manifested at the organism level are measured by clinical parameters, laboratory studies, and radiologic measurements that aid in designing tailored therapy in order to achieve maximal treatment outcome. The other view (also called zoom-in view) stems from laboratory research, in which response to a drug can be studied at the gene, protein, or cellular level by using high-throughput technologies such as integrated genomic microarray expression profiling coupled with pathway network modeling. Generally, a systems approach that integrates knowledge from analyses across multiple zoom levels is likely to uncover new target(s) in a pathway of interest that probably would have been left undiscovered using traditional techniques.

Most targeted drugs currently used in the clinic have been designed to affect a single protein, or in some cases multiple kinases. Unfortunately, even with the most specific drugs, additional proteins or related pathways may also be involved (off-target effects). Systems pharmacology categorizes these off-targets into two types: (1) off-targets that result in unwanted drug effects and (2) secondary targets that enhance the desired drug effect (24). These secondary targets exist within a complex network that determines the balance between therapeutic and adverse effects. Understanding the beneficial secondary targets of targeted drugs is likely to provide valuable information for designing personalized therapies on the basis of the host’s molecular make-up and, eventually, aid in the rational design of multitargeted therapies using multiple drugs selected on the basis of synergy, or near-synergy, in their effects. Such an understanding requires cell-based studies coupled with robust, computational tools to obtain irrevocably strong proof for the integration of pathways involved in the observed synergy. One such approach involves the use of network modeling that provides mathematically and statistically robust information about the involvement of effector networks in the interaction between multiple drugs. These network models can also predict key secondary targets of drug interactions, thus, uncovering previously unrecognized targets that may be useful for future drug development in cancer. On the basis of network modeling and systems-level analyses, more than 100 drug synergistic cases have been recently reported or are currently being commercialized. For example, in a recent study, the identification of expression signatures predictive of sensitivity to the Bel-2 family member inhibitor ABT-263 in small cell lung carcinoma and leukemia and/or lymphoma cell lines has been documented (25). This study revealed that global expression data could identify key gene expression patterns for sensitivity to ABT-263 in small cell lung carcinoma and leukemia and/or lymphoma, and may provide guidance in the selection of patients in future clinical trials. Other rationally designed studies, based on extensive knowledge of the pathways, have recently been reported for metastatic breast cancer. In this case, the role of EGFR, the cyclo-oxygenase (COX-2), and the matrix metalloproteases 1 and 2 (MMP-1, MMP-2) were found as the key genes that trigger lung metastasis, and further documented a significant reduction in lung metastasis when the cells were treated with the anti-EGFR antibody cetuximab, the COX-2 inhibitor celecoxib, and the broad-spectrum MMP inhibitor GM6001 (26). Supported by this information and other excellent examples, we undertook a systems-level approach in combination with network biology to identify and validate potential targets in the synergistic combination of a novel small molecule inhibitor of MDM2 and oxaliplatin in pancreatic adenocarcinoma.

Proof of Concept: Using a Systems Biology-Based Approach to Predict Potent Drug Combinations

Our laboratory has been focused on delineating the molecular mechanism(s) of action in pancreatic adenocarcinoma, and recently has been working on a specific small molecule inhibitor (MI-219) of MDM2. The MI-219 is a specific, orally active, MDM2 inhibitor that binds to the p53 binding pocket of MDM2 and disrupts the MDM2-p53 interaction leading to apoptosis (the structure of MI-219 is given in Figure 1 and reported previously; refs. 27–29). Recently, we have observed that MDM2 inhibitor synergizes with chemotherapy, leading to enhanced growth inhibition and apoptosis in pancreatic adenocarcinoma cells. Interestingly, 50% of wt-p53 tumor-bearing mice treated with this combination remained tumor free without recurrence for 120 days (30). Our most recent study also showed a synergistic enhancement of MI-219 activity in the presence of zinc (31). Overall, our published results indicate that MI-219 can be used in conjunction with chemotherapy; however, the precise mechanism of this
synergy has not been fully characterized at the molecular level. Given the complex network of interaction between MDM2 and p53 that ultimately governs apoptosis, it is reasonable to speculate that analyzing the local network of crucial members may influence or help predict the cellular response to MI-219. In the case of MI-219, elucidating important key proteins and/or pathways will help us in identifying patients who are more likely to respond to MI-219 treatment, which will provide molecular guidance for conducting rationally designed combination trials. We have used this model to validate the applicability of a systems approach in predicting potent drug combinations in pancreatic adenocarcinoma and obtained critical information toward understanding the mechanism for this synergy, which serves as a proof of concept for launching any future clinical studies.

Microarray profiling of a wt-p53–containing pancreatic adenocarcinoma cell line (Capan-2) treated with either MI-219, oxaliplatin, or their combination, revealed some very interesting results that may have clinical implications. Capan-2 cells were purchased from American Type Culture Collection. The cell lines have been tested and authenticated in our core facility, Applied Genomics Technology Center at Wayne State University, as late as March 13, 2009. The method used for testing was short tandem repeat profiling using the PowerPlex 16 system as March 13, 2009. The method used for testing was short tandem repeat profiling using the PowerPlex 16 system from Promega. Global analysis of genes showed that MI-219 treatment resulted in the alteration of only 48 genes, which highlights the targeted nature of MDM2 inhibitor MI-219. On the other hand, oxaliplatin is a cytotoxic agent and caused alteration of 761 genes. The combination of MI-219 with oxaliplatin resulted in 767 genes being altered. The most important aspect of this finding is the emergence of 286 synergy–specific unique genes that were not found in the MI-219 alone or in the oxaliplatin–treated group (Fig. 2A). This finding confirms that the synergy between MI-219 and oxaliplatin is at the gene level. Principle component analysis showed that the global gene signatures between single treatments versus combination treatments were nonoverlapping and could be differentiated at different time points (Fig. 2B). Molecular network modeling of a total of 767 gene–associated pathways revealed a total of 22 statistically enriched functional groups that were linked to biologically distinct functional pathways (Fig. 3A). Interestingly, network modeling of the 286 synergy–unique genes showed statistical enrichment of 14 disease (cancer) relevant pathways (Fig. 3B). This finding suggests that these pathways are relevant to cancer, further indicating that the combination synergy between MI-219 and oxaliplatin is at the gene level, comprising distinct biologically meaningful processes. Further analysis of the combination treatment network revealed the presence of several local networks, or hubs, rather than a single hub of activity interconnecting MDM2-p53 (Fig. 4). Central players such as the CREB binding protein (CREBBP; i.e., ubiquitously expressed gene) that is involved in the transcriptional coactivation of many different transcription factors, including p53 (32), collaborates/cooperates with ARF (CARF) that is responsible for p53 stability (33), and NF-kB and early

Figure 2. Gene expression microarray profiling and molecular network modeling predicts synergy between two drugs at the gene level. A, a Venn diagram showing synergy between MDM2 inhibitor MI-219 and oxaliplatin. Note emergence of 286 synergy–unique genes in the combination group. B, principle component analysis showing global gene patterns postdrug treatments: single treatment versus combination at different time points. The analysis is representative of biological triplicates of Capan-2 pancreatic adenocarcinoma cells 1) untreated; 2) MI-219 treated (15 μmol/L); 3) oxaliplatin treated (15 μmol/L); and 4) MI-219 (15 μmol/L) + oxaliplatin (15 μmol/L) combination treatment for 16 and 32 hours. RNA quality was assessed by Agilent Bioanalyzer 2100 RIN analysis. Expression levels at each time point and treatment were determined by microarray analyses using the human HT12 array. Data were processed for quality control and normalized across compared arrays by quantile normalization. Genes with 1.7 or greater expression fold change at any time point in the series were included in Ingenuity Pathways analyses. Cluster analysis of expression profiles was done with Bayesian analysis using GAGED software. Canonical pathways analysis identified the pathways from the Ingenuity Pathways analysis library of canonical pathways that were most significant to the data set. Molecules from the data set that met the 1.7 fold-change cut-off and were associated with a canonical pathway in Ingenuity’s Knowledge Base were considered for the analysis. The significance of the association between the data set and the canonical pathway was measured in two ways: 1) a ratio of the number of molecules from the data set that map to the pathway divided by the total number of molecules that map to the canonical pathway; 2) Fisher’s exact test was used to calculate a P value determining the probability that the association between the genes in the data set and the canonical pathway is explained by chance alone.
growth response protein (EGR1) tumor suppressor module (34), all of which are known to positively affect p53 reactivation, which in principle would drive cells toward increased apoptosis. Most importantly, these observed gene changes could also be validated at the mRNA and protein level (data are not shown and are beyond the scope of this review article).

Taken together, these results show a rich pattern of interactions between MI-219, oxaliplatin, and their targets, and further confirmed that the observed synergy is indeed at the gene level. Such a vast amount of information about the mechanism involved could be useful in predicting response to MI-219–oxaliplatin synergy, and certainly validates the applicability of this technology in understanding drug target gene signatures. It is believed that such information will aid in the design of clinically successful drug combinations for complex diseases such as pancreatic adenocarcinoma, and will ultimately improve the overall survival of patients.

Implications for the Treatment of Pancreatic Adenocarcinoma

Our intended goal in using network modeling and systems analysis was to show as a proof of concept the applicability of such an approach in understanding the synergy between MI-219 and oxaliplatin at the gene level, and to further identify crucial driver pathways that augment p53 reactivation-mediated events. Consistent with our intended goals, we observed that, in addition to the
genes mentioned above, our analysis revealed a prominent role for hepatocyte nuclear factor 4 alpha (HNF4α; ref. 35), which modulated a totally distinct, yet p53-linked, set of proteins driving apoptosis (MI-219 single treatment 16 and 32 hours; Fig. 5A and B). In the combination network analysis, significant downregulation of HNF4α target genes was observed (Fig. 5C, shown in green). This downregulation was concomitant with upregulation of CARF, EGR1, HIF-1α, ETS transcription factor, and E-cadherin. The identification of HNF4α as a key player was interesting because it has not been well defined in pancreatic adenocarcinoma cells used in this study (Capan-2 cells with wt-p53 gene). Nevertheless, published data have shown that HNF4α is highly expressed in pancreatic tumors compared with their normal counterpart (Fig. 5D; ref. 36). The HNF4α is known to interact with the p53 positive regulator CREBBP (37), which underscores its role in augmenting apoptotic effects in this synergic combination. In summary, these findings support newer applications of this systems approach in determining the drug target gene signatures and providing information on potential newer targets that could be further studied, either as biomarkers or molecules worthy of therapeutic targeting.

**Conclusion**

Biological interaction networks have been available to the scientific community for nearly a decade, but the concept of network biology has found its application in...
the area of drug discovery only in the last 5 years. Despite being imperfect and error-prone, the initial version of human interactome networks (38, 39) are of sufficient quality to provide clinically useful information. Such integrated analyses may lead to the identification of pathways, and targeting these pathways may lead to synergy between drugs, or add to the effect of a given drug. Thus far, network analysis has facilitated the prediction of possible molecules affected by specified perturbations of up- and downstream targets by different drugs. Such predictions can be applied to developing clinically relevant drug combinations, and were recently validated by a systems-based approach using MI-219 (in this review) and ABT-263 (25). Network modeling and systems biology are still in their infancy, but have the potential to provide a major contribution to the advancement of personalized medicine. It is expected that the completion of disease-related interaction maps and the phenotypic effects of targeting multiple proteins in model organisms with chemical probes will soon permit refinement of systems biology models to the point in which they can be routinely applied to some of the most important areas of drug development. In conclusion, we advocate the use of this systems biology approach to further understand multiple drug combinations currently being tested in different cancers. Such cutting-edge knowledge is anticipated to improve the rational design of combination therapy, and will hopefully improve the overall outcome of treatment, especially for pancreatic cancer, a disease for which better treatment is so urgently needed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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