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Systems Pharmacology for the Study of Anticancer Drugs: Promises and Challenges

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Systems pharmacology (SP) is an emerging branch in the field of pharmacological science that applies systematic approaches to the study of pharmacology with an aim to provide a holistic understanding of mechanism of action of drugs on various levels of biological system. SP is a discipline bridging systems biology and pharmacokinetics-pharmacodynamics (PK-PD) to enhance systematic understanding of the efficacy and side effect of existing drugs in order to identify predictive biomarkers for treatment outcomes and targetable pharmacophores for drug discovery [1,2]. Network analysis is the main approach to studying SP with a focus on identifying desired and undesirable targets within the networks of diseases and drug responses, including chemicals, proteins or nucleic acids. The successful application of network analysis to SP relies on the advance of computational analysis techniques and the availability of high throughput biological data on drug discovery generated by "omics" studies, such as genomics, proteomics, metabolomics and transcriptomics [2,3]. Ultimately, network analysis could provide global views on drug-target relationships and intertwining interactions among cellular pathways in physiological and pathological processes [4-6]. Systems pharmacology approaches have recently been implicated in the studies of anticancer drugs, especially in new drug discovery and understanding of variability in responses to chemotherapy, by providing insights systematically into the relationships between tumour phenotypes, oncogenes and drug targets.

Identification of valid drug targets is perhaps the biggest challenge in drug discovery and a key factor attributable to high attrition rates in clinical trials, especially for complex diseases such as cancer. Traditional approaches of anticancer drug discovery are mostly based on compound libraries, combinatorial chemistry and high-throughput screening, which are generally empirical and lack of direct targeting strategy [7]. SP may overcome these obstacles to increase the efficiency of identifying drug targets through its holistic nature and huge data handling capacity over traditional methods. Several recent studies have shown this advantage in identifying potential novel targets for anticancer drug discovery. A systematic analysis has identified 434 human proteins that are targeted by 989 of FDA-approved drugs, including receptors, enzymes and transporters [8]. Notably, receptor tyrosine kinases are the third largest receptor target class among them and frequently targeted by anticancer agents. This information is important for studying interactome networks of drug-target interactions using topographical analysis for target prediction [9]. Protein-protein interaction (PPI) network is a framework for identifying new target in drug discovery. Chu (2008) constructed apoptosis networks of PPI in normal and cancerous cells based on microarray data of cervical cancer HeLa cells, online interactome databases BIND, HPRD, Intact and Himap, using the Osprey program. Seventeen proteins belonging to six categories have been identified as potential drug targets, with BCL2 ranked as the highest among several new drug targets, including BAK1, CASP2, BCL2A1, IGF1, PRKCD, NFKB1 and PCNA [10]. Rosado and co-workers (2011) reported a systems pharmacology-based study of clinical chemotherapeutic drugs for gastric cancer, including combinations of 5-fluorouracil (5-FU)-doxorubicin-methotrexate, 5-FU-etoposide-folic acid, docetaxel-cisplatin-5-FU, FOLFOX and XELOX, to identify chemoresistance-related targets and other novel targets. For these drugs, they have identified total 417 nodes and 3,830 edges distributed to five sub networks. In their study, ~10 major bottlenecks were identified based on the analysis of network centrality, global topology and gene ontology of PPI and compound-protein interactions, including NDC80, RXRA, AURKB, GRB2, RASA1, TP53, MAPK8, and STMN1[10].

A SP-based network analysis has identified determinants of chemoresistance and chemosensitivity of 12 chemotherapy drugs clinically used in gastrointestinal cancer based on the data from microarray, proteomics, next-generation sequencing and metabolomics [11], and it suggested several novel drug targets. For instance, a number of genes related to cell proliferation, protein and fatty acid metabolism, and cell adhesion as indicators for selection of anticancer drugs in gastric cancer, including genes encoding proline, glutamate and 1-acyl lysophosphatidylcholines as indicators for 5-FU [12], aurora kinase B and ELOVL5 fatty acid elongase for cisplatin, fucosyltransferase 2 (FUT2), lectin, galactoside-binding, soluble 4 (LGALS4) and cadherin 17 for 5-FU and oxaliplatin [13]. A comparative proteomics study revealed that baculoviral IAP repeat-containing 6 (BIRC6), an apoptosis inhibitory protein, as a key determinant for the sensitivity of colon stem cell resistance to oxaliplatin and cisplatin, which could be explored as a potential therapeutic target [14]. Therefore, SP-based integration of these omics data with computational modelling provides an opportunity to identify chemotherapeutic drug targets for drug discovery and predictive diagnostic markers, such as the 14-3-3β as a biomarker for 5-FU response in gastric cancer [15] and surviving as a target for development of global pathway inhibitors in cancer [16]. In another recent study, systems pharmacology and cellular pharmacology have been combined successfully to explore the cellular targets that are associated with the preventative effect of mifepristone, a clinically used synthetic steroid abortifacient drug, on tumour

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metastasis in breast cancer [17]. The integrative network analysis identified 47 mifepristone-related hub genes and focal adhesion kinase (FAK)-associated signalling associated with cancer metastasis using the Natural Language Processing, gene ontology hierarchy and KEGG pathway enrichment analysis, followed by *in vitro* verification of the inhibitory effect of mifepristone on cellular migration and adhesion in human breast cancer MDA-MB-231 cells, by suppressing the expression of FAK, paxillin and the formation of FAK/Src/Paxillin complex [17].

SP has also been applied in cancer research to assist understanding of the apparent inter-patient variability in their response to the majority of chemotherapy, which is a major problem in oncology clinics. For instance, Yang et al. (2010) reports a mechanistic, quantitative and probabilistic SP approach to investigating this problem based on genomics data [18]. Integrative network analysis has been suggested to analyse drug response data through constructing the landscape of phenotype-genotype relationships for banks of tumour cell lines based on the expressing profiling and sequencing, and measurement of diverse responses of individual cell lines, in this way, data-driven, multiscale mathematical models that link patient dosing to drug concentrations in tumour cells can be established in order to understand the relation between cell-to-cell variation and patient responses [18].

Systems pharmacology-based mathematical modelling of biological processes at cellular level has advantages over conventional physiologically based pharmacokinetic models in deciphering signalling networks and identifying potential therapeutic targets for drug discovery [19,20], including anticancer drugs. An earlier study has established a validated mathematical model of Ras GTPase signalling module in cancer cells and identified a strategy to develop molecular targeted anticancer drugs that could cause stronger inhibition on the cancerous Ras network than on the wild-type network [5]. Benson et al. (2012) reports a two-compartment systems pharmacology-based mathematical model to determine the affinity and kinetics of ligand-receptor binding of receptor tyrosine kinases, which play critical roles in many types of disease such as cancer, pain and neurological disorder. This SP model captures the biological cross-membrane dynamics by modelling the intracellular and extracellular domain of tyrosine kinase receptors in different compartments. It is a valuable tool to depict ligand-receptor systems by simulating the effects of drug intervention and ways of administration on cross-membrane signalling through receptor tyrosine kinases [21]. Gallo (2013) advocates a systems pharmacological approach to investigating the disposition of low-molecular-weight tyrosine kinase inhibitors (TKIs) in tumour tissue based on the combination of physiologically based pharmacokinetic model and cell-specific enhanced pharmacodynamics model (PBPK/ePD) [22]. This PBPK/ePD model incorporates tumour compartments, including vascular, interstitial fluid and intracellular compartment, to quantitatively characterize drug disposition and dynamics of TKIs at cellular levels. This approach is important in development of personalized chemotherapy as it can predict tumour heterogeneity-related time-dependent dynamics of cellular drug concentrations of tyrosine kinase inhibitors [23].

In summary, SP has the potential to make a significant impact on our systematic understanding of mechanisms and new drug discovery for anticancer drugs, despite of numerous challenges in implementing computational methodology to biological, physiological and pharmacological data. For instance, there are some practical problems in performing SP-based network analysis for certain anticancer drugs or malignant cellular pathways, including the lack of number and validity of specific microarray databases, proper comparison between cancerous and normal cells, and inadequate time-points to reflect the dynamic nature of drug-target interactions. In addition, current SP-based studies are mostly based on the data generated by approaches of systems biology, which are unable to provide sufficient pharmacological information for a valid modelling and network analysis for specific anticancer drugs. Because of the unique safety risk of anticancer drugs, it remains a challenge to predict adverse effects that may arise when targeting a specific protein due to the heterogeneity of protein hubs in different cancer types. Nevertheless, it still represents a promising and rapidly evolving era for the application of systems pharmacology in anticancer drug research. Increasing number of databases and computer-based tools are publically available for conducting SP studies, such as the interactome protein-protein and small molecule-protein databases at STITCH 2.0 and STRING 8.3, Molecular Complex Detection program, Cityscape network analysis program and a recently reported web-based DTome tool for interactome construction [24]. Another opportunity for the SP-based studies of anticancer drugs is to focus on the difference of expression profiles of target proteins between cancerous and normal cells and tissues to increase the selectivity of new drugs, which is impossible to be solved in traditional methods of drug discovery.

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