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Mini Review

Development of Fangjiomics for Systems Elucidation of Synergistic Mechanism Underlying Combination Therapy

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ABSTRACT

The rapid development of omics technology provides an opportunity for fulfilling the understanding of the synergistic mechanism of combination therapy. However, a systems theory to analyze synergy remains an ongoing challenge. Fangjiomics is a novel systems science based on a holistic theory integrated with reductionism which has been utilized to systematically elucidate the synergistic mechanisms underlying combination therapy using multi-target-, pathway- or network-based quantitative methods. Besides, our ability to understand the polyhierarchical structure in synergy is driven based on multi-level omics data fusion in Fangjiomics. According to the basic principle of "*Jun-Chen-Zuo-Shi*", further global integration across various omics platforms and phenotype-driven quantitative multi-scale modeling would accelerate development in Fangjiomics-based dissection of synergy in multi-drug combination therapies.

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1. Introduction

The development of omics technology has already facilitated significant advances in our understanding of complex diseases, and has also promoted the transformation of drug discovery paradigm, from original "single-gene, single-target, single-drug" to "multi-targets" of drug combination [1–5]. Due to its improved efficacy and reduced side effects, combination therapy is considered a promising strategy for combating complex disorders, including malignancy [6,7], postoperative vomiting [8], hepatitis C [9], and etc. Drug combination aims to exert its synergistic effect, a phenomenon of super-additivity of biological response to compounds applied jointly [10], to provide many therapeutic benefits, such as increasing drug sensitivity [11], shortening the onset time [12] as well as reducing side effects [13].

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Nevertheless, it's still a challenge to reveal the synergistic mechanism of combination therapy. Recently, the strategy used in prior studies was to analyze the effect of two drugs on a certain signaling receptor [14], enzyme [15], nucleotide [16] or process [17]. For example, synergistic reexpression of tumor suppressor gene, secreted frizzled-related protein 1 (sFRP1), was observed in combinatorial drug-treated groups of histone deacetylase (HDAC) inhibitor romidepsin and methyltransferase inhibitor [18]. However, the synergistic effect of most drug combinations for the treatment of complex diseases is produced via modulating multi-targets or multi-pathways [19]. Based on large-scale generation and integration of omics profile data, such as transcriptomic, proteomic, metabolomic, and phenomic data, we are able to interpret the synergistic mechanism of combination therapy in a more reasonable manner. Network pharmacology provides us an approach to integrate multi-omics data, which can not only offer a systems-level understanding of drug action and disease complexity but can also help to improve the efficiency of target selection and drug design [20,21]. Nevertheless, recent network analysis mainly focuses on a certain omics level rather than the whole human body, and it's difficult to identify the patterns of drug combinations. Fangjiomics, first proposed by Prof. Zhong Wang in 2011 [22], based on a holistic view, is to study the drug combination pattern by firstly collecting scattered knowledge together to build a whole system and then making qualitative or quantitative analysis using array-designed dimensionality reduction. Network analysis is an applicable but not the only mode for the study of Fangjiomics. By fusing multi-omics data, Fangjiomics can be used to investigate the structure of multi-ingredients as well as the compatibility mechanism. "*Jun-Chen-Zuo-Shi*" is one of the principles in Chinese medicine to reveal the drug combination pattern with the analysis of Drug-Drug Interactions (DDIs) and drug-symptom response in a prescription (Fangji). This principle could be also used to systematically explain the mechanism of drug combinations in Fangjiomics. The sovereign *(Jun)* aims at the primary pathological symptom of a disease, playing a critical role in the treatment; while the minister *(Chen)* is to enhance the action of the sovereign; the assistant *(Zuo)* may exert supplementary assistant or supplementary inhibitory effects (the former is to treat other secondary symptoms of the disease, while the latter is to restrict the toxicity induced by the sovereign and minister); and the envoy *(Shi)* is to deliver all the drugs to where the disease is. This basic idea in Fangjiomics may provide cues about the different functional orientations of different drug combinations. This mini-review describes the characteristics and application of Fangjiomics, which is able to uncover the synergistic mechanism of drug combinations at transcriptomics, proteomics, metabolomics and multi-omics levels.

2. The Characteristics of Fangjiomics

Fangjiomics, as a new field of science, involves molecular biology, molecular pharmacology, bioinformatics, chemical biology, systems biology, traditional Chinese Medicine (TCM), Chinese Materia Medica, and many other disciplines. In contrast to traditional omics techniques on a certain level of cell, tissue or organ, this holistic therapeutic strategy forms rational drug combinations by integrating diverse omics data such as genomics, transcriptomics, proteomics and metabolomics [23]. Different from traditional pharmacological models, Fangjiomics has 6 specific features [22]: 1) its rationale originates from a holistic theory integrated with reductionism; 2) it assumes that the multiple biological effects of drug combinations are related to multiple genes, multiple targets and multiple pathways; 3) it supports patient-centered care, in compliance with the strategy of translational medicine, i.e. "bedside to bench, and then bench to bedside"; 4) it uses multiple microcosmic therapeutics with different activities (with different molecular targets) which are originated from real-world clinical practice; 5) it focuses on multiple outcomes based on the spectrum of ingredients instead of using a single pure chemical to produce a single outcome; and 6) it systematically develops multiple modes of array-designed combination therapies, such as "magic shotgun", vertical, horizontal, focusing, siege and dynamic arrays [23].

Moreover, several strategies could be used in combination therapy to enhance efficacy and reduce toxicity in Fangjiomics, such as mutual synergy (MS, Xiangxu), mutual assistance (MA, Xiangshi), mutual restraint (MR, Xiangwei), and mutual neutralization (MN, Xiangsha) [22]. MS means that two components with similar properties are combined to reinforce their actions, whereas MA indicates that one component in the combination is the leading substance and the other plays subsidiary roles to strengthen the action of the former. Both strategies may lead to synergistic or addictive effects. MR and MN are two strategies used to attenuate or eliminate toxicities. Besides, mutual inhibition (MI, Xiangwu), which means that one component in the combination may weaken the effect of the other one, as well as incompatibility (IM, Xiangfan), which suggests inappropriate combination due to increased toxicity, are consistent with the concept of antagonistic drug-drug interactions (DDI) in modern pharmacology, both of which would be not discussed in this mini-review.

3. Systematic Assessment of Synergistic Mechanism in Fangjiomics

In this post-omics era, Fangjiomics introduced multi-omics technology, as genomics, transcriptomics, proteomics or metabolomics, etc., to systematically analyze synergy effect and discover more effective combination regimens to achieve the goal of higher efficacy and lower toxicity. Systematic assessment in Fangjiomics integrates macroscopic description on the roles of the constituent drugs in synergy with microscopic analysis of the synergistic patterns of massive biomolecules at the omics level. Based on a holistic theory integrated with reductionism, we developed a profile-effect-dependent analysis in Fangjiomics to uncover the synergistic mechanism underlying combination therapies, which target on multiple pathways, sub-networks via different array modes.

3.1. Advances in Pathway-based Analysis of Synergistic Mechanisms

3.1.1. Vertical Hit on the Same Pathway

Whole-transcriptome sequencing (WTS) of xenografts has been used to explore the molecular impact of imatinib mesylate (IM) and MK-2206 (an AKT inhibitor) on gastrointestinal stromal tumor (GIST) response. The results showed that this drug combination upregulated two neural genes, also known as tumor-suppressor genes, i.e. brain expressed X-linked 1 (BEX1) and neuronal pentraxin 1 (NPTX1), which could affect tumor cell fate by shifting the pro/anti-apoptotic balance towards cell death, and expressing its significant synergistic effects in a series of IM-sensitive and resistant GIST cell lines [24]. It is considered a powerful and rational preclinical treatment for GIST. The characteristic effect of the drug combination on multiple genes in the up-down context of pro-apoptotic pathway represents the "vertical array" mode in Fangjiomics. (Fig. 1A) Terpenoids and flavonoids, both of which were the extract of rabdosia rubescens (RRE), demonstrated the synergistic effect in the treatment of prostate cancer. Using the gene microarray analysis, compared with oridonin (a kind of flavonoids) alone, the RRE combinations regulated more genes of NF-κB pathway controlling inflammation and oxidative stress to inhibit prostate cancer cell proliferation [25].

3.1.2. Horizontal Hit on Different Pathways

Synergistic effect is proposed to be reflected in the activity of core pathways under different treatment conditions of jasminoidin (JA), ursodeoxycholic acid (UA) and combination groups (jasminoidin and ursodeoxycholic acid, JU), respectively [26]. Based on the multiple-pathway-dependent comparison analysis (MPDCA), jasminoidin contributes more important pharmacological effect in the combined

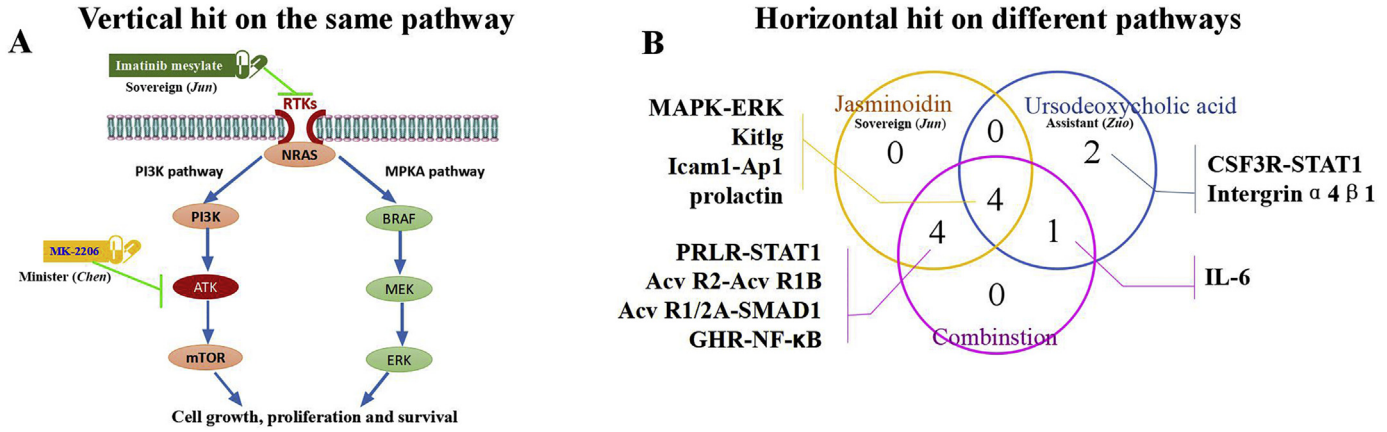

Fig. 1. Pathway-based analysis of synergistic mechanisms. A. Imatinib mesylate (IM) and MK-2206 (an AKT inhibitor) respectively act on the receptor tyrosine kinases (RTKs) and the protein kinase B (ATK) in the same pathway of PI3K to express significant synergistic effects, in which IM plays as a sovereign (*Jun*) and MK-2206 as a minister (*Chen*) [24](2017; 23 (1):171–80). The characteristic effect of the drug combination on multiple targets in the up-down context of pro-apoptotic pathway represents the "vertical array" mode in Fangjiomics. B. The Venn diagram shows the overlapping and unique of biological pathways respectively targeted by jasminoidin (JA), ursodeoxycholic acid (UA) and the combination (JU). JA acts as a sovereign (*Jun*), while UA acts as an assistant (*Zuo*) [26](2011; 667(1–3):278–86).

treatment as jasminoidin regulated over 80% of the pathways that the combination group mediated, indicating that the combination horizontally hit on different pathways. (Fig. 1B) The combination of colistin and doripenem was proved the synergistic effect against *Acinetobacter baumannii* in a metabolomics study. These two drugs perturbed various parallel pathways associated with cell envelope biosynthesis, including glycerophospholipids (GPLs), fatty acids (Fas), lipopolysaccharide (LPS) and peptidoglycan biosynthesis. Colistin acts as a sovereign (*Jun*), while doripenem as a minister (*Chen*) [27].

3.2. Development in the Theory of Network-based Synergistic Targets

The call for combination therapy on fungal infections, especially invasive fungal infections, is due to the refractory condition and scarcity of therapeutic drugs [28,29]. By using RNA-seq and network-based analysis, it was found that amphotericin B (AMB) and iron chelator lactoferrin (LF) could serve as a synergistic treatment solution in a focusing array [30]. In AMB monotherapy, increased expression of genes involved in iron homeostasis and apoptosis was observed, including cytoplasm-to-vacuole targeting (CVT) pathway, protein kinase A (PKA) signaling, and adenosine triphosphate (ATP) synthesis-coupled electron transport. By contrast, the combined treatment of AMB and LF led to a reduction in the expression of genes associated with zinc homeostasis and adaptation to zinc deficiency, as well as decreased expression of genes involved in iron uptake, PKA signaling and ATP synthesis. Combination therapy also resulted in decreased gene expression in multiple oxidative stress response pathways, including the down-regulated pathways associated with sulfate assimilation and tumor specific antigen 1 (TSA1) and regulated by Zap1p [30]. Besides, AMB could also impair the integrity of cell membrane and cell wall, and accelerate the entry of LF into cells. Once there, LF could disrupt intracellular targets that generally control intracellular iron and zinc levels in response to AMB stress, reflecting their synergistic effect. Thus, in this combination, AMB acts as a sovereign (*Jun*) drug and LF as a minister (*Chen*) which facilitates AMB to fight against fungal infections (Fig. 2A).

Using unlabelled quantitative shotgun proteomics and synthetical bioinformatics, the synergy of heat shock protein 90 (Hsp90) inhibitor and fludarabine (2-FaraA) was demonstrated as a siege array mode [31]. The proteins of breast cancer gene 1 (BRCA1), cyclin D1 (CCND1), myelocytomatosis oncogene cellular homolog (MYC), nucleolin (NCL), nuclear factor-kappa-B p100 subunit (NFkB2 p100), BID, and fas-associated factor 2 (FAF2) correlated with the accentuation of DNA damage response and apoptosis, could synergistically kill mucoepidermoid carcinoma 1 (MEC1) cells. Moreover, 2-FaraA could decrease the effective dose of the Hsp90 inhibitor SNX-7081 and alleviate the toxicity of SNX-7081, providing an alternative treatment for chronic lymphocytic leukemia (CLL) patients with p53 mutations (Fig. 2 B-C). Therefore, SNX-7081 and 2-FaraA, which play the role as a sovereign (*Jun*) or a minister (*Chen*), respectively, strengthen each other's efficacy to reverse CLL, and this combination strategy could be considered as MS (Xiangxu).

3.3. Polyhierarchical Dissection of Synergy Based on Multilevel Omics Data Fusion

Panomics, a type of omics dataset, can be used to analyze multidimensional omics data [32]. The ultimate goal for integrated genomics is the discovery and application of novel markers and targeted therapies, driving the use of "precision drugs" according to the patient-to-patient variation [33]. An experimental research in vivo and vitro suggested that the combined use of imatinib (IM) and arsenic sulfide [As4S4 (AS)] could reduce the tumor burden and prolong survival without obvious cardiac toxicity, showing a synergistic effect in the BCR/ABL-positive mice to treat chronic myeloid leukemia (CML) with increased efficiency and reduced toxicity. Using a systematic analysis on dynamic changes of the proteome, phosphoproteome, and transcriptome in K562 cells after monotherapies of AS or IM and combination treatment of AS and IM, it was found that the co-treatment led to the block of the cell cycle, reduction of BCR/ABL activity, as well as the activation of endogenous and extrinsic apoptotic pathways through complex modification of transcription and protein levels. The key pathways related to such a synergistic effect included phosphoinosmde-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/MTOR) pathway, ubiquitin proteasome pathway, and apoptotic pathway [34,35].

A systems-level approach comprising phosphoproteomics, transcriptomics and chemical proteomics [36] was applied to elucidate the novel synergistic mechanism of danusertib and bosutinib. This approach displays the hierarchical relationship among the data about proteome-wide measurements of drug-binding using chemical proteomics, global monitoring of alterations in phosphorylation states in response to drug treatment and genome-wide transcriptomics. Integration of the multilevel omics data enabled the elucidation of the mechanism by which a new drug synergy targets the dependency of BCR-ABLT315I CML cells on c-Myc through nonobvious off targets.

Yinchenhao Tang (YCHT), is one of the most famous Chinese herbal formulae to treat jaundice and liver disorders, including *Artemisia annua* L., *Gardenia jasminoides* Ellis, and *Rheum palmatum* L. The main active

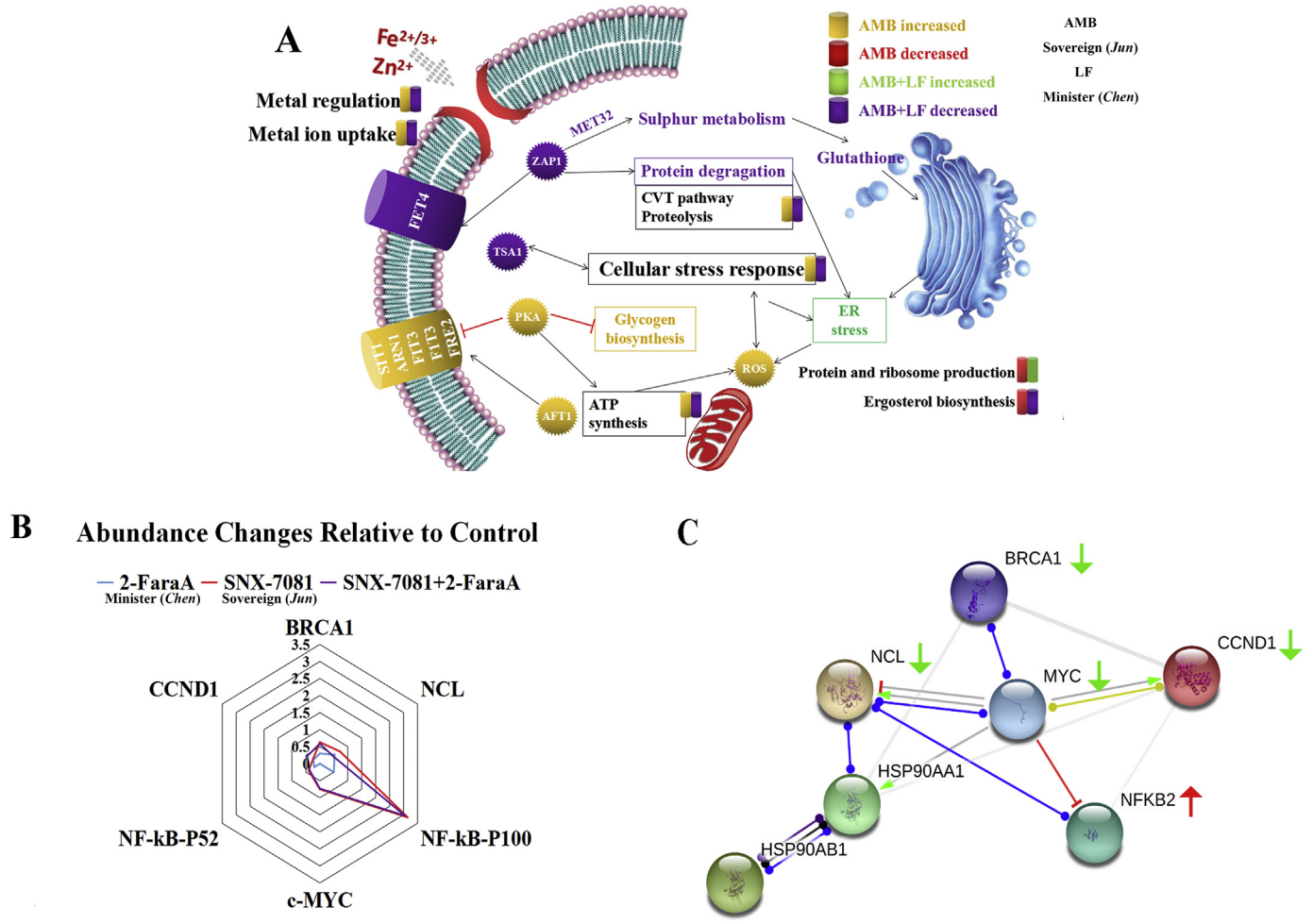

Fig. 2. Network-based synergistic targets analysis developed in Fangjiomics. A. The synergistic mechanism underlying the cellular response to AMB-LF with general dysregulation of metal ion homeostasis and appropriate cellular stress response networks. Among them, AMB plays a major role as a sovereign (*Jun*), and LF acts as a minister (*Chen*) to enhance the efficacy of the sovereign. Arrows represent the direction of regulation, and arrow with blunt end represents inhibitory signal. Yellow color indicates significant increases in the expression of gene or process induced by AMB; red indicates significant decreases in the expression of gene or process induced by AMB; green denotes significant increases in the expression of gene or process induced by AMB-LF combination; purple represents significant increases changes in the expression of gene or process induced by AMB-LF combination. The Figure is modified from the pictures published in Scientific Report [30] (2017; 7: 40232). B. The synergy effect of the combination is mostly attributed from SNX-7081 according to the proteins expression profiles of BRCA1, NCL, NF-kB p100/p52, MYC and CCND1 in MEC1 cell. C. The network with key proteins regulated by the combination of SNX-7081 and 2-Fara A is constructed by STRING 10.5. The combination of SNX-7081 and 2-Fara A accentuated the DNA damage compounded by the loss of checkpoint regulators BRCA1 and CCND1, and trigger the cell death following a loss of MYC and NCL and an accumulation of NFkB2. SNX-7081 acts as a sovereign (*Jun*), while 2-Fara A acts as a minister (*Chen*). The Figures B&C are respectively drawn according to the results published in Oncotarget [31] (2015;6(38):40981–97).

ingredients of these three herbs are 6,7-dimethylesculetin (D),geniposide (G), and rhein (R), respectively. The synergistic efficacy of DGR compounds was systematically analyzed from immunohistochemistry, biochemistry, metabolomics and proteomics and molecular network. Among them, D plays a major role as a sovereign drug, while G and R serve as the minister (*Chen*) and assistant (*Zuo*) [37].

4. Progress in Quantitative Holistic Models for Elucidating the Synergy

Since 2011, many quantitative models in Fangjiomics have been developed to quantify the global changes of omics profiles treated with drug combinations and the dynamic process of multiple nodes in the network. According to targeting patterns of synergistic drug combinations, these models could be classified into three categories, i.e. multi-target based, pathway-based, and network-based, as listed in Table 1.

Global similarity index (GSI) [39], a model of cosine coefficient similarity, is used to quantify the genotypic outcomes of gene expression profiles. A mechanistic pan-cancer pathway model was assembled with six created "submodels" to capture the regulation of stochastic proliferation and death by pan-cancer driver pathways [42]. Besides, a semi-supervised learning model of RACS (Ranking-system of Anti-Cancer Synergy) was developed to improve drug synergy prediction and markedly reduce the experimental prescreening of existing drugs despite of the unclear synergistic mechanism [43]. More promisingly, Network-based Laplacian regularized Least Square Synergistic drug combination prediction (NLLSS), could be used to predict potential synergistic drug combinations by integrating different kinds of information such as known synergistic drug combinations, drug-target interactions, and drug chemical structures [45].

5. Discussion and Perspective

Currently, most studies mainly focus on the synergy of two drugs, but the efficacy of dual combination may be unsatisfactory for certain diseases due to their poor prognosis and high-risk complications. Multi-drug combination, more in line with clinical practice, should be the future trend of combination therapy. It has been shown that the triple-drug combination, clotrimazole, mirtazapine and plerixafor, may synergistically inhibit C-X-C chemokine receptor 4/C-X-C motif

Table 1
The newly developed holistic models for synergistic mechanism in Fangjiomics.

	Models	Description	Data set	Applications	Findings
Multi-target based	A systems-level approach [36]	A multilevel experimental approach that includes proteome-wide measurements of drug-binding using chemical proteomics, global monitoring of alterations in phosphorylation states in response to drug treatment and genome-wide transcriptomics.	Phosphoproteomics; transcriptomics; chemical proteomics	Elucidation of the mechanism by which a new drug synergy targets the dependency of certain cells on a certain target protein through nonobvious off targets.	Danusertib and bosutinib targeted MAPK pathways downstream of BCR-ABL, resulting in impaired activity of c-Myc.
	A leave-one-out (LOO) Spearman rank correlation [38]	The correlation between genes and treatment.	Transcriptomics; mutation data; copy number data	Statistical analysis for identifying the correlated genes.	Olaparib (Ola) and AsiDNA suppressed the recruitment of repair enzymes to DNA damage sites.
	GSI (Global similarity index) [39]	Cosine coefficient similarities in microarray among the global gene expression patterns between two treated groups.	Genomics	Quantification of the genotypic outcomes based on gene expression profiles.	The GSI between addictive and synergistic drugs treated-group (JA + UA) was 0.57 and 0.81,, respectively; lower than JA,UA treated-groups(0.68) and JA,BA treated-groups(0.91), indicating that the gene expression variation of the synergy effect is greater than that of the additive effect.
Pathway-based	A mechanistic pan-cancer pathway model based on chemical kinetics approach [40]	A systematic model assembled with six created"submodels" (the RTK-Ras-Raf pathway, the PI3K-AKT-mTOR pathway, cell cycle pathways, and p53-DNA repair pathways, apoptosis pathways, and gene expression and degradation processes.)	Genomics; transcriptomics; proteomics	Capturing the regulation of stochastic proliferation and death by pan-cancer driver pathways.	Tailoring the model to an alternate cell expression and mutation context, a glioma cell line, allows prediction of increased sensitivity of cell death to AKT inhibition.
	MPDCA (Multiple-pathway-dependent comparison analysis) [26]	A method that ranks and compares the candidate pathways based on the coexpression genes of different groups	Genomics	Exploring the various potential core pathways	Jasminoidin possibly contributes more important pharmacological effect in the combined treatment as jasminoidin regulated 80% of the pathways that the combination group mediated.
	A kinetic model of Ras/RAF /MEK/ERK and PI3K/ PTEN /AKT signaling [41]	A computational model describing the response kinetics of the signaling network to HRG -induced HER3/HER2 receptor heterodimerisation and the effect of HER2 inhibitor on ERK and AKT activation	Genomics	Understanding the mechanisms of combination anti-HER2 drug effects in terms of reprogramming of the RTK signaling networks following mono- and combination therapies.	Trastuzumab and pertuzumab alone and in combination differentially suppressed RTK network activation depending on RTK co-expression.
Network-based	NIMS (Network target-based Identification of Multicomponent Synergy) [42]	An approach to transfer the relationship among agents to the interactions among the targets or responsive gene products of agents in the context of a biological network specific for a disease or pathological process.	Agent genes and agent phenotypes manually collected from PubMed and the China National Knowledge Infrastructure(CNKI)	Prioritizing the synergistic agent combinations in a high throughput way.	The NIMS outputs can not only recover 5 known synergistic agent pairs from 63 agents on a pathological process instanced by angiogenesis, but also obtain experimental verification for synergistic candidates combined with.
	RACS(Ranking-system of Anti-Cancer Synergy) [43]	A semi-supervised learning model to address the limited positive/ labelled samples and the large set of unknown /unlabelled combinations, which combines features of targeting networks and transcriptomic profiles.	Transcriptomics; drug pharmacological characteristics; drug targeting networks	Drug synergy prediction despite of the unclear synergistic mechanism.	Using data on human β-cell lymphoma from the Dialogue for Reverse Engineering Assessments and Methods consortium, we show a probability concordance of 0.78 compared with 0.61 obtained with the previous best algorithm.
	Enhanced Petri-Net (EPN) model [44]	In EPN, drugs and signaling molecules are assigned to different types of places, while drug doses and molecular expressions are denoted by color tokens. The changes of molecular expressions caused by treatments of drugs are simulated by two actions of EPN: firing and blasting.	Genomics	Prediction for the synergistic effect of pairwise drug combinations from genome-wide transcriptional expression data, by applying Petri-nets to identify specific drug targeted signaling networks.	The synergistic predictions using EPN are consistent with those predicted using phenotypic response data. The molecules responsible for the synergistic effects with their associated feedback loops display the mechanisms of synergism.

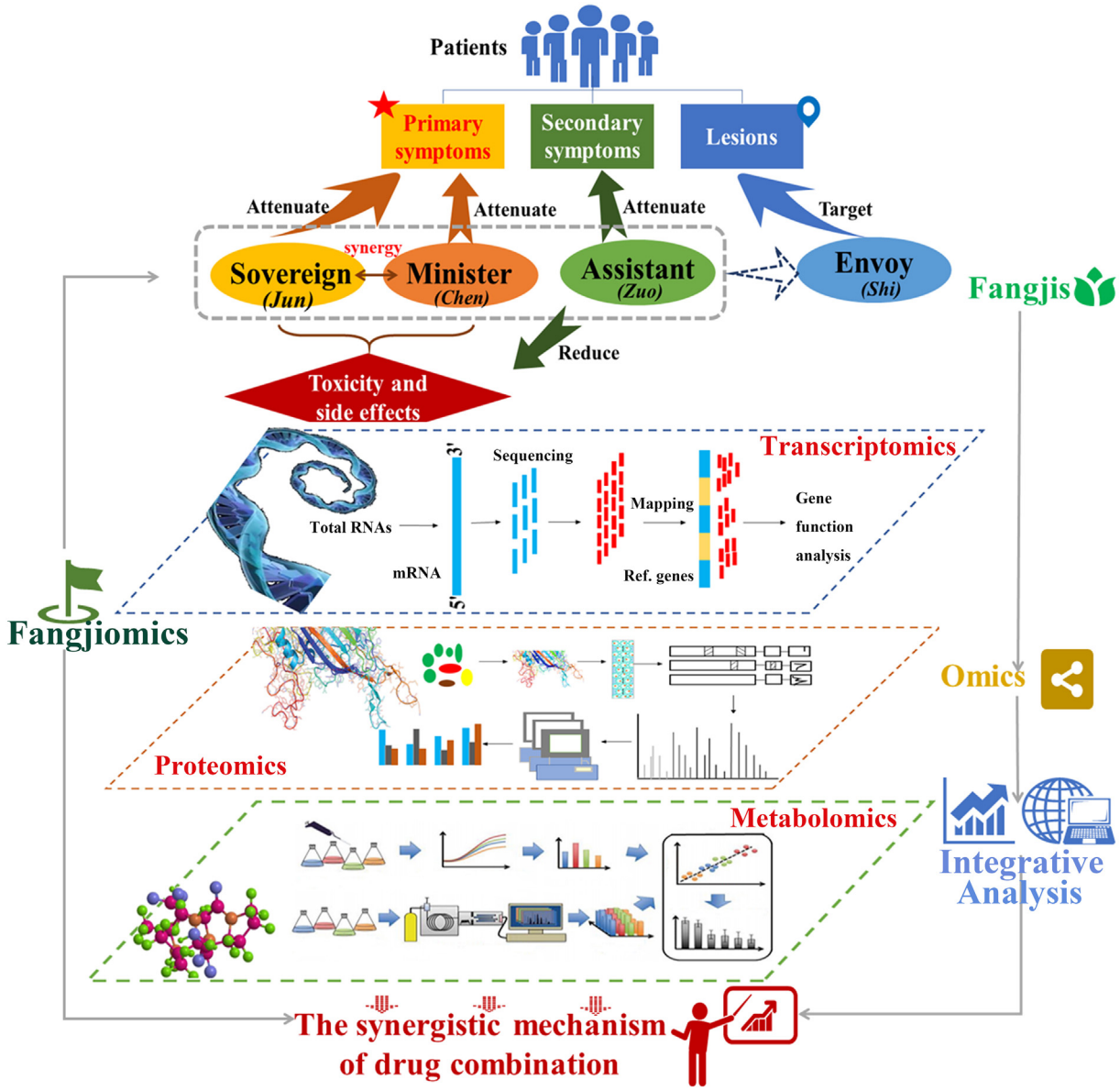

Fig. 3. The Fangjiomics-based paradigm for future research on synergistic mechanism of drug combination. After fusion of multi-omics profiles, phenotype-dependent synergistic mechanism can be uncovered according to the basic principle of "*Jun-Chen-Zuo-Shi*" in Fangjiomics.

chemokine12 (CXCR4/CXCL12) signaling more completely than any monotherapies during the cytotoxic treatment of glioblastoma [46]. In another study, a quadruple-drug regimen, gemcitabine, 5-fluorouracil, leucovorin and cisplatin, was designed to maximize sequence-dependent synergy, attempting to minimize toxicity of the four drugs [47]. However, the theory and the mechanism underlying multi-drug combinations still remain an ongoing challenge. With the fusion of omics technology, Fangjiomics can be used to study the structure of multi-ingredients and the compatibility mechanism. Fangjiomics not only focuses on the integration of holistic and reduction analysis for signaling pathways and network targets, but also uncovers the potential inter-pathway and inter-target relationships, which may provide insights into clinical use of drug combinations. According to the basic principle of "*Jun-Chen-Zuo-Shi*" in Fangjiomics, each ingredient in a combination could be classified into 1 of the 4 types: "sovereign" (*Jun*), "minister" (*Chen*), "assistant" (*Zuo*), or "envoy" (*Shi*), which may target the primary or secondary symptoms to deal with the complicated disorders [48]. This basic idea in Fangjiomics may provide cues about the different functional orientations of different drug combinations (Fig. 3). According to our previous studies on Qingkailing injection, jasminoidin (JA), baicalin (BA), and ursodeoxycholic acid (UA) are the main effective compounds in this injection, where JA plus UA shows a synergistic effect, while JA plus BA shows an addictive effect [26,39,49,50]. Using mechanism analysis at the levels of genes, pathways and networks, we discovered that JA exerted the main effect as the sovereign (*Jun*), BA as the minister (*Chen*), and UA as the assistant (*Zuo*) [26,39].

Through multi-scale interventions, Fangjiomics-based combination therapy appears to be a promising strategy which integrates multiple omics data to uncover the synergistic mechanism of drug combinations in treating complex diseases. However, although network models are proposed to fuse the multi-omics data by linking genes, proteins and metabolites through the edges that represent multiple biological relationships [51] to analyze the mechanism of drug combinations [52], due to network complexity and lack of guidance on the top-level design, it is very difficult to simplify drug-drug synergistic network. The network should be divided into different sub-networks associated with certain biological functions. Here, the basic classification principle of

"*Jun-Chen-Zuo-Shi*" in Fangjiomics could be introduced to explore the correlation between drug reactivities and phenotypes by analyzing their targets on primary or secondary symptoms (Fig. 3). This phenotype-dependent spectral-effect or network-effect pharmacological mechanism analysis may better reduce the dimension of high-dimensional pharmacological network to reveal the mechanism of drug combinations based on multiple omics platform. In the future, building dynamic response system based on large-scale human biological information using the technologies in this big data era, may provide more ideas for the evaluation and confirmation of network [53]. For example, in the theoretical framework of Fangjiomics, quantitative time-series data combined with qualitative network mathematical model may pave a new way to describe the overall dynamic regulation of the human body. As data continues to grow in size and complexity, there is much anticipation in exploiting deep machine learning [54] and artificial intelligence [55] to curate integrative multi-omics data to refine the current medical practice and promote precision medicine in the near future.

Conflict of Interest

We declare no conflict of interest.

Author Contributions

Zhong Wang and Jun Liu conceived and designed the research; Peng-lu Wei and Hao Gu drafted the manuscript, and Jun Liu and Zhong Wang revised the manuscript. All authors have reviewed and revised the manuscript.

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