Systems Biomedicine Acts as a Driver for the Evolution of Pharmacology

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Short Communication

Pharmacology has evolved over the years. Describing the explicit effects of biologically active chemicals originally, this scientific discipline now explores the biological effects of drugs at the molecular level. In the last decade, functional genomics data and systems biology outlook did lead this evolvement. On the other hand, the role of systems outlook gradually increases through improving existent approaches and developing novel concepts in order to provide possible solutions to the grand challenge in pharmacology, i.e. the development of efficient treatment strategies for tackling the complexities of the diseases.

The development of novel and effective treatment strategies for complex pathophysiologies, such as cancers, requires an understanding of the generation and progression mechanisms. RNA-level analyses generate new information that can help in understanding the mechanisms behind disease pathogenesis to identify new biomarkers and therapeutic targets and to enable drug discovery [1]. Whole RNA sequencing, coding and non-coding RNA expression array datasets have been used to illuminate the mechanisms of disease processes, and have identified mRNAs, miRNAs, and lncRNAs associated with disease progression as possible drug targets [2-4]. All these findings provide evidence for the importance of integrative approaches within the systems biomedicine concept in future pharmacological research. Integration of total RNA-seq datasets (coupled with data from other omics level analyses) with biological network models will provide molecular signatures, which may be used for screening and therapeutic purposes, will be beneficial for understanding etiopathogenesis and biological mechanisms of the diseases, and for developing effective and safe medications.

As our knowledge on the biological mechanisms of the diseases is increased, there still exist challenges in identifying appropriate targets for complex diseases. Systematic screening of different molecules to identify candidate drugs with activity against single therapeutic targets and pathway components has been accepted as the main strategy in drug discovery during the past decade. However, targeting individual elements of pathogenic pathways is mostly not an efficient strategy to overcome the complexities of the disease state. Instead, recent advances in systems biomedicine researches presented methods to identify set of biomolecules (genes, proteins, lipids, metabolites, etc.) combined with a certain expression pattern, which could be considered as "systemic signatures" or "systems biomarkers" that represent the molecular reprogramming of the cell in response to any perturbation [2,5-7]. Therefore, these signatures (acquired via analysis of high-throughput data from next generation technologies) should be considered as proxies of pathologies to generate hypothesis for drug discovery process. A recent example is the ovarian cancer specific gene module consisting of 84 prognostic genes, which was differentially co-expressed, and co-regulated in ovarian cancer [8]. The leading idea here is that the certain co-expression pattern in the module can be evaluated together with the mode of action of the drug candidate, and if they are sufficiently negatively correlated (i.e., the exposure to drug reverses the expression pattern observed in disease state but not in healthy state), then it is reasonable to hypothesize that the drug might be able to revert the disease signatures and hence the disease phenotype itself [9]. In the case of a new drug candidate with unknown mode of action, the expression profiles before and after drug exposure can quantitatively assess the changes brought by the drug on the transcriptional re-programming of the gene module. Therefore, differentially co-expressed gene modules might provide new insights on the development of new drugs, allow following the effect of drugs on cellular machinery, and accelerate the drug repositioning studies.

Nowadays, drug repositioning (or repurposing) has appeared as a promising strategy besides

drug development process which is a resource-intensive, time-consuming and costly. R&D investments on pharmaceutical industry take billions of dollars and more than ten years to bring a new drug to the market. Unlike these drug development challenges, drug repositioning suggests recycling the existing drugs for use in new clinical indications so that this method provides drug candidates with known established formulations, extensive pharmacokinetics, toxicity, clinical trial and post-marketing surveillance safety data. The drug repositioning is also considered as an essential strategy for cancer patients since conventional chemotherapy drugs, such as DNA damaging agents, have notorious side effects that significantly reduce the quality of life of patients. As most of the non-cancer drugs have little or tolerable side effects in human, repurposing of non-cancer drugs for anticancer therapy will be an outstanding approach. At the age of the omics sciences and bioinformatics, rational drug repositioning approaches are being developed to determine candidate molecules as drug targets and potential drugs considering data from different omics levels as well as the disease-gene-drug (DGD) triad. Especially, clinical genomic and transcriptomic data were evaluated within a comprehensive, systematic, and integrative analysis framework applied to various disease conditions [10]. On the other hand, the strength of genome-scale biomolecular networks (such as metabolic, signaling, and transcriptional regulatory) on analysis of molecular signatures in disease states have already been shown [4,11-13]. These models will also be useful to predict potential drug targets and analyze drug signatures at a molecular level. Reinforcement of the present hypothesis generating tools with genome-scale biomolecular networks might promote the efficiency of the predictions. In addition, integration and analysis of data from other omics levels, such as micro biome, might accelerate the discovery of safer and more efficacious drugs, since gut micro biota harbored by healthy and diseased individuals are diverse and altered in the disease state. Besides their essential functions such as food digestion, pathogen protection etc., gut micro biota has a critical role in efficiency of drug response both directly and indirectly. Hence, diet has also great impact on the gut micro biota, pioneering computational models comprising xenobiotic metabolism and microbial enzymes known as modifying drugs, should be constructed to integrate diet-micro biota-drug interactions [14]. In addition, bacteria found in soil and marine environments have long been known to generate small molecules (e.g., peptides) to regulate or fend off fellow microbes and mediate host-organism responses to their presence. Indeed, such molecules have been a major source of antibiotics and other drugs. Micro biome studies comprising all of the genetic material within a micro biota can be carried out and precise antibiotics may be repurposed for complex diseases in the end. On the other hand, lipid metabolism is mainly affected in cancer cases. Therefore, lipidomics may also be another emerging approach used for drug repurposing. Improved biotechnology as well as accumulated biotechnological data on metabolome, lipidome, micro biome etc. makes current drug repositioning strategies evolved and in the future, personalized and precision medicine will be merged with drug repositioning strategies to find the best treatment options specific per person, ultimately.

The field of systems level analysis in pharmacology is still in its infancy. In the future, its outcomes will allow not only the development of tailored drugs to treat a wide range of health problems, but also the construction of mathematical models that predict and explain the behavior of biological systems subjected to naturals and/or synthetic drug molecules.

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