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Role of Molecular Biology in Elucidating Drug Action, Tolerance and Susceptibility

Shiny Jacqueline L*

Department of Biotechnology, I.K. Gujral Punjab Technical University, Punjab, Jalandhar, India

Commentary

This commentary focuses on the molecular biology aspects of drug action and its relevance to the current research and development activities for drug designing and development for treatment of various diseases and disorders. In general the fundamental mechanism for treatment of a disease lied in the interaction of the drug molecule with the target proteins that are related to the phenotype of the specific disease. The concept of one-gene, one-drug, one-disease had been challenged many times. In fact one drug can act on multiple targets thus enabling drug repurposing for the treatment of new diseases and finding new indications for the existing developed rug molecule. However there is also the possibility of interaction with other molecules leading to undesirable side effect due to the complex cellular and molecular biological factors. Deeper understanding of the cellular and molecular biology under normal and disease metabolism allows us to understand how the drugs target the disease phenotype and how the genetic and protein mechanism of the cell responds and their mutual interactions. Focus on such research activities could provide us new insights at the molecular biology level on finding new indications for the existing drug molecule. For the computation analysis and simulations prove to be very effective and accurate predictions of any such interactions and outcomes. The pharmacokinetic and pharmacodynamics aspects of drug interactions are modulated by the molecular biology of the cell and such complex interaction could be efficiently handled using computation and bioinformatics approaches. More importantly the drug chemical configuration lone cannot be sufficient to predict the physiological effects as the drugs are subject to complex metabolic transformations within the cell.

The drug repurposing can be done wither by finding the common chemical active site and by common characteristics of different disease. Another method could be the analysis of the gene expression profiles in conjunction with the phenotypic profiles of different diseases that represent within the characteristic features of the disease. Such analysis of the drug and disease data can be complementary and can overcome the missing knowledge of drug pharmacology and can potentially yield additional drug targets. With the availability of large data sets it is now possible to construct functional genetic networks with higher accuracy and completeness. High throughput genetic expression analysis, sequencing and whole genome analysis provides better and accurate understanding of the drug action and its side effects. Such studies have revealed that propranolol has potential inhibitive action on cancer proliferation and Telmisartan had therapeutic effect by inhibiting the defective signaling in Alzheimer's disease.

Over the recent years it was found that the rate of new drug approvals is slowing down despite increased emphasis on drug discovery and development. This is mainly due to complex pathophysiology of the disease that are redundant and robust to alterations caused by single molecular target of the drug molecule. To overcome this limitation, combination drugs are being proposed. If selective drugs are used in combination therapy then the chances for drug side effects are minimal. In order to treat hypertension thiazide diuretics are used however the drug causes hypokalaemia which can be prevented with the use of angiotensin converting enzyme inhibitors if used simultaneously. Breast cancer is resistant to Trastuzumab and the simultaneous use of Saracatinab can improve the drug efficiency. For the treatment of type 2 diabetes glyburide and metformin are used simultaneously and they act in different ways, glyburide reduces the insulin resistance while metformin increases the insulin secretion and this combinatorial therapy improves the therapeutic efficiency of as the complement the mechanisms.

There is a greater need to evaluate the molecular biology and the physiological response of drug action in order to use the combinatorial treatment and propose new combined drug treatment dosage and period of treatment. Evaluation of the physiological pathways and the signaling pattern are very important for computer based modeling and simulations. Complex chronic diseases require such combination therapies for efficient treatment and complete remission. For example anti-Parkinsonian drugs such as Permax and Dostinex activate dopamine receptors and also 5-HT2B serotonin receptors, resulting in adverse effect on valvular heart disease and thus limiting its use. Therefore in such cases multiple drugs may be required for prevention of side effects.

Drugs that are either in the form of synthetic chemical compound or a biological protein regulates the biological process and makes alterations. Conventionally a small drug molecule may have the molecular weight of 500 Daltons and several of the developed compounds have higher molecular weight. Cellular and molecular based assays are fundamental for the development of novel drug molecules. Genetic screening, biochemical and cell based assays are used for evaluation of the target and interference cell components. Molecular biology enables the understanding of the binding and target compounds. The molecular pathways help in the screening and the identification of the target proteins. Molecular biology based on the biophysical and biochemical methods help us elucidate the molecular interactions and the mechanism of action of the target and drug compounds.

To assess the complex biological responses that the drugs elicit in human beings are identified using a large data sets of drug induced transcriptional modules from genome wide microarray data of drug treated human cell lines and its characterization. Similar studies are conducted in different cell lines. Such analysis helps in the identification of the gen functions and novel cellular and molecular

***Corresponding author:** Shiny Jacqueline L, Department of Biotechnology, I.K. Gujral Punjab Technical University, Punjab, Jalandhar, India, E-mail: shinyjacqueline@gmail.com

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regulators of gene function and physiology, inhibitors of cell cycle, new modulators of receptor functions. All these are possible from the molecular studies and improve our understanding of the molecular basis of drug actions.

Molecular biology studies are also essential for characterization of deciphering the anti-biotic drug resistance mechanisms in tolerant pathogenic microorganism strains. Such studies include the characterization of cell wall alterations, activation of the efflux pumps, transcriptional regulons, alterations in the metabolic flow and modification of the molecular defense machinery.