EDITORIAL

Precision Medicine in Pharmacometrics and Systems Pharmacology

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Fueled by the pan-cancer genomics landscape, druggable targets discovered in The Cancer Genome Atlas (TCGA), and great successes of clinically actionable pharmacokinetic variants, precision medicine is one of the driving forces for biomedical research. It is becoming a reality to benefit patient care. Pharmacometrics and systems pharmacology are critical for precision medicine research, and are making a number of key contributions. The impact can be broadly categorized into the following areas: omics data, drug data, and clinical data integration; target selection, drug selection, dose selection, and precision medicine clinical implementation.

OMICS DATA, DRUG DATA, AND CLINICAL DATA INTEGRATION

There are three major data types that need to be integrated for precision medicine research: omics, drug, and clinical. Each data type itself has two forms. One form is the raw data, for example, omics and clinical data collected from patients. The other form is the derived, or summarized data, such as a genetic effect on a drug response published in an article.

Each data integration scheme has its own purpose. For precision medicine clinical implementations, the targets (e.g., genomic variants, proteins, etc.) need to have validated function information. Drugs and their targets shall be validated in vitro and in vivo. Clinical data, including both efficacy and adverse drug events, shall reflect their definitions in clinical trials and/or prospective/retrospective pharmaco-gene-tics studies. On the other hand, if the data are integrated for precision medicine research, the data integration scheme shall be more comprehensive. For example, both genomic variant location annotations and functional annotations shall be collected, and all preclinical and animal studies of drug potency and efficacy data shall be included. Soysal et al’s article is an excellent example of how various drug databases can be integrated to facilitate personalized oncology research.

TARGET SELECTION, DRUG SELECTION, AND DOSE SELECTION

One of the major findings from TCGA is that many cancer types share the same somatic mutations. Many of them are the drug targets. Therefore, in current precision medicine clinics, especially in cancer treatment, off-label drug usage is becoming a routine practice. However, limited evidence sources to support the off-label drug usage creates a challenge. Because of the newly available cancer cell line drug screening data and omics data, some initial evidence of off-label drug use from one cancer type to the other cancer types are becoming available. Considering multiple potential drug targets revealed in the genomics profiles from the same patient, more sophisticated systems pharmacology models are needed to integrate pathway data for prioritizing the target selections. Because of the high frequency of multitargets identified from a cancer patients’ genome, multitarget therapies are the trend in cancer research. Therefore, in order to understand whether drug combinations lead to changed pharmacokinetics drug concentration or side effects compared to the single drugs, pharmacometrics (i.e., pharmacokinetics drug interaction models) and systems pharmacology models will be highly valuable to address the dose selection. Interestingly, herbal medicine has its own unique strength in drug repositioning, because it is usually safe, and it can hit several targets at the same time. Fang et al. demonstrate a very interesting and powerful systems pharmacology approach to repurpose nature products for precision oncology.

PRECISION MEDICINE CLINICAL IMPLEMENTATION

The ultimate goal of precision medicine is to improve patient care. Even with well-integrated omics, drug, and clinical data, there are some challenges in precision medicine clinical implementation. First, genetic effects on drug response are not yet fully integrated with other risk factors to assist physicians to make clinical decisions. Second, the overwhelmingly rich genomics data and clinical annotations become an enormous barrier for a physician to digest the information and communicate their decisions with patients. It calls for a user-friendly interface to visualize the integrated omics, drug, and phenotype data. This is where the pharmacokinetics, pharmacodynamics, and disease progression models can make a major contribution to integrate all the risk factors to predict both efficacy and side effects at the same time.

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