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A Systems Biology Approach to Pharmacogenomic Discovery

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The individual response to therapeutic treatments is likely to be a complex trait that is controlled by various genetic and non-genetic factors. In an ideal world of personalized medicine, the information about a patient's genetic make-up or gene expression profile would be considered by physicians together with other clinical information (e.g., age, gender) to tailor medical care for both maximizing effective therapy and avoiding adverse effects. The challenge for personalized medicine is particularly urgent for cancer chemotherapy. Clinically, anticancer drugs often present a narrow therapeutic index, indicating that small changes in dosage could cause severe toxic response (e.g., neurotoxicity and nephrotoxicity) [1,2] with the extreme end of complication resulting in fatality. Therefore, understanding the comprehensive relationships between genetic/non-genetic factors and drug response is a critical step toward the realization of personalized medical care in clinical oncology.

During the past decade, high-throughput technological platforms have become available for comprehensively and quantitatively profiling genetic variation and molecular targets in cells. For example, the advances in microarray (e.g., the Affymetrix GeneChip and the Illumina BeadChip platforms) and RNA-sequencing (e.g., the Illumina Genome Analyzer) technologies have allowed the profiling of the entire transcriptome (i.e., mRNA-level expression) of cells including both common and rare transcripts, as well as transcript variants (i.e., transcript isoforms). For genetic variation, large research efforts such as the International HapMap Project [3,4] and the 1000 Genomes Project [5] have made publicly available a detailed map of human genetic variation across major populations including Asians, Europeans and Africans. Taking advantage of these technological and research advances, cell-based pharmacogenomic studies have begun to identify genetic determinants that are responsible for drug response [6,7].

Particularly, the model using the lymphoblastoid cell lines (LCLs) from the HapMap Project [3,4] samples has proved to have significant advantages (both scientific and ethical) in pharmacogenomic discovery [6,7]. Compared with the traditional candidate gene approaches, pharmacogenomic studies using the resources of the HapMap samples (e.g., genotypes of >4 million singe nucleotide polymorphisms [SNPs], copy number variants [CNVs], and whole-genome gene expression profiles) [8] could comprehensively investigate the relationships between, for example, genetic variation and drug response, as well as gene expression and drug response, at the genome-wide level. For example, by integrating the whole-genome gene expression data (~9,000 expressed genes generated by the Affymetrix Human Exon Array) [9,10] and the SNP genotypes from the HapMap Project [3,4], a number of genetic variants, acting through gene regulation (i.e., eQTLs: expression quantitative trait loci), have been identified to be associated with the cytoxicities to some anticancer drugs, including etoposide [11], daunorubicin [12], carboplatin [13], cisplatin [14] and Ara-C (cytarabine arabinoside) [15] in a panel of LCLs derived from individuals of African and European ancestry. Recently, using the LCL model, CNVs were also identified to predict cellular sensitivity to an array of chemotherapeutic agents of heterogeneous molecular therapeutic action (e.g., cisplatin, carboplatin, daunorubicin, etoposide) [16]. In addition, genome-wide meta-analysis using these resources facilitated the identification of variants associated with platinating agent susceptibility across human populations [17].

The current progress in pharmacogenomic discovery demonstrates the promise of integrating what we have learned from these studies to construct a more comprehensive model that may predict individual response and toxicity to anticancer drugs. A systems biology approach that aims to integrate and analyze the complex datasets from a pharmacogenomic model such as the HapMap samples would ultimately allow researchers to assemble the puzzle of individualized drug response. A major breakthrough could be driven by the deeper understanding of gene regulation mechanisms. Since gene expression is a complex and quantitative trait that is regulated by various genetic and non-genetic factors, besides genetic variation (e.g., through eQTLs), other important epigenetic mechanisms (e.g., microRNAs, DNA methylation, and histone modifications) could also play critical roles in regulating gene expression, thus potentially affecting the downstream phenotypes of variation in drug response. We expect that the beginning of the availability of microRNA [18,19] and DNA methylation [20,21] profiles using high throughput technologies on these samples will help provide novel insights into both the general mechanisms of gene regulation and how the cells respond to therapeutic agents. For example, the availability of genome-wide DNA methylation profiles will allow us to evaluate the contribution of mQTLs (methylation quantitative trait loci) to the variation in drug response. Besides two-dimensional relationships between molecular target profiles and drug response, a systems biology approach will be necessary to evaluate the complex networks of gene-gene and gene-environment interactions that may contribute to drug response as well. Furthermore, the recent development in technology has begun to allow high-throughput profiling of other dynamic components in cells (e.g., lipidome, glycome, metabolome, rare and transient transcripts). We expect that a systems biology approach to pharmacogenomic discovery will be able to integrate and analyze all of these complex datasets for the aim of elucidating the underpinning mechanisms of drug response in the future. In addition, the current pharmacogenomic resources (e.g., PharmGKB, PACdb) [22-24] will need to be integrated to provide much easier access to a variety of relevant datasets (e.g., drug response phenotypes, gene expression, and genetic variation data). A central portal for systems medicine may be our goal for this purpose of data integration.

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Though significant challenges remain to be dealt with (e.g., bioinformatic tools for analyzing and integrating data with increasing complexity and size), we are cautiously optimistic that the realization of personalized medicine in clinical oncology will be possible through a multi-disciplinary, systems biology approach to pharmacogenomic discovery. No doubt, *Internal Medicine* will be a high-quality venue for investigators and clinicians interested in using system biology approaches to personalized medicine. We look forward to sharing your research results, ideas and perspectives in this exciting field.

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