

The Recent Advances and Future Perspectives of Personalized Medicine

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Introduction

We are in the middle of the revolution of medical care. With the development of pharmacogenomics in recent years, personalized medicine becomes more and more available in clinic for patients' care. Pharmacogenomics studies the variation of genes in human genome that may be used to predict responses to a specific drug or class of drugs. Traits such as drug responses may be determined by environmental factors as well as genetic influences. Genetic polymorphisms can account for 20-95% of variability in drug disposition and effects [1]. For example, the anticoagulant warfarin had a 20-fold difference in the dosages to achieve the desired therapeutic effect when given to different patients [2]. Personalized medicine proposes the customization of patient care. Medical decisions, practices, and products are precisely serviced for the individual patients according to their molecular diagnosis and genetic makeup. Biomarkers have been widely searched from diagnosing foetal genetic diseases, assessing risk for cardiovascular diseases to predicting treatment response of chemotherapeutic agents for cancers.

The successful completion of the Human Genome Project (HPG) was regarded as one of the greatest scientific achievements in the last 50 years. Human haplotype map of over 3.1 million single nucleotide polymorphisms (SNPs) was also finished in 2007 [3]. The protein-coding genes in the human genome could be important targets for drug development. Genome-wide association study (GWAS) is a powerful approach for identifying the genetic causes of complex traits. More than 2,000 robust associations with more than 300 complex diseases and traits were identified in recent years by GWASs [4]. One of the strengths of GWAS is that many novel genes that were never suspected to have roles in the diseases were identified. The classic example is ORMDL3 gene on human chromosome 17q21. It was not regarded as an asthma candidate gene until the polymorphisms of ORMDL3 were found to have association with asthma in a first-generation GWAS of approximately 1000 children with asthma and 1000 controls [5]. GWAS also identified some common novel genes in different diseases. e.g. SMAD3 and DENNDB1 have been implicated in Crohn's disease and asthma; ORMDL3 with ulcerative colitis and asthma [6]. These results suggest an overlap in some of the inflammatory mechanisms influencing these diseases and provide the common ground for therapeutic solutions for the diseases.

The Recent Advances in Personalized Medicine Research

Cancers are the leading causes of death worldwide and are complex heterogeneous diseases. Selective biological therapies have now emerged to effectively treat certain types of cancers. In Clinic breast cancer can be subdivided according to HER2 expression, PI3KCA

mutations and BRCA1/2 mutations [7]. Lung adenocarcinoma is divided according to EGFR mutation, EML4-ALK translocation, MET amplification, HER2 amplification, FGR4 amplification and KRAS mutation [8]. The genotypes or expression profiling greatly influence that chemotherapy and targeting therapy of the cancers. For instance activating mutations in EGFR have sensitivity to EGFR tyrosine inhibitors, but the secondary mutation T790M in exon 20 makes inhibitors ineffective [9]. KRAS mutations are almost exclusively detected in codons 12, 13, and 61 of exon 2. These mutations significantly associated with lack of response to treatment with the anti-EGFR monoclonal antibodies (mAbs). KRAS mutations have also been established as potential biomarkers for predicting the efficacy of anti-EGFR mAb in colorectal cancer [10]. In metastatic colorectal cancer, the outcome of the patients treated with first-line 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) was determined by the genotyping for KIR-HLA pairs [11]. Chromosome 17 short arm deletions are a hallmark of high-risk multiple myeloma. Most of the deletions include TP53. Patients with chromosome 17 deletions have a more aggressive disease, characterized by a shorter time to relapse, extra-medullary disease and central nervous system involvement [12]. More recently, interest in immunotherapies including inhibiting specific checkpoints involved in cancer immune evasion has demonstrated promising activity in patients with metastatic renal cell cancer [13].

Not only for cancers, personalized medicine also made progress for other chronic diseases. Human airway diseases such as asthma and chronic obstructive pulmonary disease (COPD) are inflammatory diseases, inhaled corticosteroid (ICS) is one of the common managements for the diseases. A study of the response of glucocorticoid therapy has shown that patients who were homozygous for allele mapped to glucocorticoid-induced transcript 1 gene (GLCCI1) had an improvement in respiratory function [14]. Recently a novel SNP, rs10044254 in the intron of the gene FBXL7 on chromosome 5 is associated to improved symptomatic response to Inhaled corticosteroids in 2 independent paediatric asthma cohorts [15]. Beta-adrenoceptor agonists (β -agonists) have been used clinically to relieve bronchoconstriction of asthma or COPD patients. The β 2-adrenergic receptor (β 2AR) is the target molecule of β 2-agonists. The gene for the receptor, ADRB2, is located on chromosome 5q31. Most clinical studies have focused on the Arg16Gly SNP of the receptor. Arg16 homozygotes had been found to have greater initial bronchodilator responses to β 2-agonists than Gly16 homozygotes in response to short-acting β -agonists [16,17]. For cardiovascular diseases, there is a class of antihypertensive drugs, β 1-adrenergic receptor blockers or β -blockers, which might be less effective in a subgroup of African American subjects for the management of congestive heart failure. This reduced efficacy might be related to variants in 2 genes related to the G protein-coupled pathway of the

β 1-adrenergic receptor (ADRB1) and G protein receptor kinase 5 (GRK5) genes. Mutations Arg389Gly on ADRB1 and Gln41Leu on GRK5 associate with a reduction in mortality in human subjects with heart failure and coronary ischemia treated with a β -blocker in different pharmacogenetic studies [18,19]. A Genome-wide scan identified a single strongly associated SNP, rs4363657 in SLCOB1B1 that was strongly associated with an increased risk of statin-induced myopathy. It is likely that genotyping of the SLCOB1B1 variants will help to achieve the benefits of statin therapy more safely and effectively [20]. Recent study analysing 1249 variants located in 57 hypertension pharmacogenes confirmed that geographic origin strongly affects hypertension pharmacogenomics variation and that 31 pharmacogenes are geographically differentiated [21]. These examples of variable drug responses in patients with respiratory and cardiovascular diseases illustrate the personalized approaches not only recognize ethnic or racial subgroups, but also identify the variants that may be responsible for the effect of drugs for the diseases.

The Future Perspectives of Personalized Medicine

The DNA variants cannot explain all the difference among individuals for the difference outcome for treatments. The development of personalized medicine also relies on the research on transcriptomic (mRNA and microRNA expression profiles), epigenomic (DNA methylation profiles), metabolites and microbiota.

Alterations in microRNAs (miRNAs) are involved in the pathogenesis of various types of diseases. Cell-free miRNAs show potential as novel biomarkers for many diseases. They can be detected in plasma, serum and other body fluids such as urine and saliva, serve as a non-invasive diagnostic tool. miRNAs also have an important role in chemo-resistance of cancer cells and could be useful predictors of therapeutic response. The expression profiling of miRNA analysis and deep-sequencing enable a comprehensive profiling of cell-free miRNAs from low amounts of RNA samples. More than 50 miRNAs have to be found associated with many kinds of cancers [22].

Metabolites such as lipoproteins and lipids can work as disease modulators and risk factors. Novel technologies permit the determination of a broad spectrum of metabolites simultaneously at high resolution. Metabolite screening can be applied in the cell level and in animal studies. It not only provides new insight of the metabolism of the gene's product but also possible identifies new biomarkers for the diseases. In cancer, the characteristic cell surface glycosylation is frequently transformed due to altered expression of glycan-modifying enzymes. Dietary intake of the non-human Sia N-glycolylneuraminic acid (Neu5Gc) also shows to natural metabolic-glycoengineering of human carcinomas that accumulate and express Neu5Gc. Research on Neu5Gc will lead to development of personalized treatment of cancers in future [23].

Epigenetics studies heritable change in gene expression cause by molecules that bind to DNA rather than changes in the underlying DNA sequence. Three main classes of epigenetic marks are DNA methylation, modification of histone tails and noncoding RNAs. DNA methylation is associated with many diseases from cancers to asthma [24]. The patterns of gene expression that determine cellular type and function become stably restricted during development, partly through methylation of CpG sequences and gene silencing. Abnormalities of DNA methylation are well recognised in single gene disorders and also in cancers. It is very likely that genome-wide studies of methylation status at various loci may identify new genes and

pathways. It is also important to recognise that age, sex, genetic polymorphisms and other environmental factors have all been strongly associated with altered methylation at selected loci. These factors will have to be taken into account if methylation changes at individual loci are to help understand complex diseases for personalized medicine.

Microbiota also plays the important roles for the development of personalized medicine. Whole microbial genome sequencing and metagenomics are revealing the extraordinary diversity of microorganisms and their vast genetic and metabolic repertoire. These microorganisms are commensal on body surfaces exposed to the external environment including the gut, respiratory tract and skin the membership of complex microbial communities can have important roles for the diseases [25].

In summary, personalized medicine has made great progress due to the expanding of pharmacogenomics research. The developments of miRNA profiling, epigenetics investigation, metabolites screening and microbiota research will make personalized medicine possible from cancers to common complicated diseases. The developments will revolutionize medical cares for patients in near future.

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