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Review



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Editor's note：*The individual differences diversify the signs of a disease，especially in the patients with cancer，which is attributed at least in part to the variation of genes. Translational medicine research may conversion of our knowledge of human genomic variation to practical application in improving health via，i. e. ，personalized diagnostic and therapeutic implications. Addressing the challenges in the context of cancer research in personalized medicine will enhance our understanding of translational medicine research.*

Demands and challenges to the personal medicine of cancer research

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Abstract　Personalized medicine is defined as "a form of medicine that uses information about a person's genes，proteins，and environment to prevent，diagnose，and treat disease" by the U. S. National Cancer Institute. The applications of personalized medicine in cancer is broad，including：evaluating the risk of developing a particular type of cancer and selecting screening strategies to lower this risk；Matching the right patients with the appropriate treatments that are more likely to be effective and reducing side effects by targeting treatment to each individual patient；Predicting the risk of recurrence and providing strategies to identify the patients who would benefit from adjuvant therapy. With the help of advanced knowledge of molecular oncology and development of new technologies，such as whole genome sequencing，SNPs analysis，DNA-microarray technology，proteomics by mass spectrometry and bioinformatics，patients may receive more effective tailored therapy that targeting the specific tumor. Although many challenges still remain，it is clear that personalized medicine will dramatically change the cancer therapy in the near future.

Key words　personalized medicine，targeted therapy，prognosis，challenges

Cancer is a serious threat to human life and health，which account for approximately 13% of all deaths each year. About 12. 7 million cancers were diagnosed and 7. 6 million people died of cancer in 2008 worldwide[1]. According

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to the World Health Organization, the global burden of cancer increases dramatically and deaths from cancer worldwide are projected to continue to rise to over 11 million in 2030.

In the past decades, most cancers are initially detected by symptom appearances or through screening tests and medical imaging. Delayed diagnosis may result in missing the appropriate timing of treatment, which increases the risk of death. Typically, cancer is treated with chemotherapy, radiation therapy and surgery. Usually, medical care for patient is based on the type and stage of the cancer. Patient who gets the same cancer almost receives the same treatment, which is so called "one size fits all". However, some patients respond well to the treatment while others do not and some patients have significant side effects while others do not. It has become clear that tumorigenesis is a multistep process, which is caused by multiple genetic defects, environment and lifestyle factors[2]. Each individual with the same type of cancer often have different genetic defects, which explains why patients respond heterogeneously. It reminds us that we need more-specific therapies targeting to each tumor. After firstly reported by Robert Langreth and Michael waldholz in 1999, personalized medicine has aroused extensive concern worldwide, which means treat people based on their individual genetic makeup[3]. Personalized cancer medicine is the use of each person's unique clinical, genetic, genomic, and environmental information to provide specific prevention, screening, and therapeutic treatment strategies of an individual cancer.

1 Personalized cancer medicine in cancer prevention and diagnosis

As a new and rapidly advancing field of healthcare, personalized cancer medicine can be used to evaluate a person's risk of cancer and to select screening strategies to lower this risk. Genetic mutations of tumor suppresser genes are always associated with high risk of cancer, BRCA1 and BRCA2 mutations are the most well-known mutations in hereditary cancer with elevated risks of developing breast and ovarian cancers[4]. As genetic test is currently widely available, person who tested with BRCA mutation could take primary prevention to efficiently lower the risk of cancer, including oral intake of sodium selenite, tamoxifen and prophylactic mastectomy[5]. The most common types of cancer that can be genetically transmitted include breast, colorectal and gastric cancers and the mutation carriers may benefit from the prevention lifestyle[6-8]. However, it is estimated that familial cancer only accounts for 5% ~10% of all cancers, while other genetic variants may be neglected in individuals without family history. Thanks to Genome-wide association studies (GWAS), scientists have identified multiple single nucleotide polymorphisms (SNPs) associated with cancer risk[9,10]. If the genetic information indicates a higher risk of developing a particular type of cancer, person with the risk may choose a lifestyle or drug prophylaxis and benefit from tailored treatments.

For decades, the tumor, node, metastasis (TNM) – staging system is a international standard for diagnosis in most solid tumors[11]. The limited information on the characteristics of tumor size, degree of invasion and metastasis obviously can not reflect the complexity of cancer and no longer enough for diagnosis in nowadays. As an adjuvant strategy to TNM staging system, molecular diagnosis is a new strategy that based on the advanced knowledge of molecular oncology and improvement of technologies. Molecular classification and staging offer much more elaborate information reflected by molecular levels of DNA, RNA and proteins. With the application of high-throughput technology, gene-expression signatures can be used as a new class of molecular diagnostic test for cancer. Cancer can be classified into subtypes by which have similarities in biological behaviors. This type of data analyses is called hierarchical clustering or unsupervised classification[12,13]. Analysis of the expression profiles of 70 kidney tumors has demonstrated that molecular profiles of kidney cancers closely correlated with their histological subtypes and could have important diagnostic and therapeutic implications [14,15]. Currently, four different molecular subtypes of breast cancer can be identified according to gene expression profiling, which include: Luminal A (ER + or PR +, HER -2 -), basal-like (ER -/PR -/HER -2 -), Luminal B (ER + or PR +, HER -2 +), and HER -2 positive (ER -/PR -/HER -2 +), each subtype is associated with different clinical outcomes[16]. Additionally, breast cancer also can be classified into subtypes by 70 - gene assay and 76 - gene assay, which can be used as a prognosis indicator[17,18]. Future more, several reports indicate that molecules in blood serum detected by mass spectrometry can reflect various stages of cancer [19,20]. It is possible that advances in personalized medicine will lead to a dramatic shift in cancer diagnosis, that cancer may be named according to its genetic characteristics instead of traditional descriptions one day.

2 Personalized cancer medicine in cancer therapy

The traditional approach to cancer therapy has provided treatment according to the morphological appearance of the tumor, but similar histopathological appearance shows significantly different clinical courses and re-

sponses to therapy. It has become clear that cancers developed from a series of genetic defects and individuals with the same type of cancer often have dissimilar genetic defects. This finding explains why patients who seem to have similar cancers respond differently to the therapy, and the understanding of molecular mechanism of tumorigensis may help to develop treatments targeting altered genes responsible for the progression of cancer. Cancer patients may be offered with personalized cancer treatments besides the standard clinical trails, such as targeted therapy. Targeted therapy is the use of medications designed to target aberrant molecular that has a critical role in the survival, growth, or metastasis of cancer cells of a certain type. For example, the epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase which can activate signal transduction pathways that are involved in the regulation of cellular proliferation, differentiation, and survival[21]. There is large evidence shows that EGFR signaling is hyperactivated in multiple types of cancer associated with poor prognosis and decreased survival, mainly due to the mutations in the kinase domain of EGFR and gene copy number variations[22]. Anti-EGFR therapies have been developed recently and wildly used for the treatment of lung cancer, colorectal cancer and pancreatic cancer[23-26]. According to the mechanisms, the antagonists of EGFR can be classified into small molecule tyrosine kinase inhibitors (TKIs) including gefitinib and erlotinib, and monoclonal antibodies (mAbs) including zalutumumab, nimotuzumab and matuzumab [27]. Other targeted therapy drugs also have been used in treatment with particular type of cancer, such as herceptin in HER2 overexpressed breast cancer and Glivec (Imatinib) in BCR-ABL fusion chronic myeloid leukemia[28, 29].

Genetic and genomic information from the individuals may help to shift the treatment to a more effective way with reduced side effects. For example, it is clear now that KRAS mutation predict resistance to EGFR targeted therapy in colon cancer[30]. Additionally, a large-scale RNA interference screen has discovered PTEN as a modulator of drug sensitivity involved in trastuzumab resistance in breast cancer[31]. The advance of DNA-microarray technology enables identification of characteristic expression patterns of large groups of genes associated with specific tumor, which are known as gene-expression signatures[13]. Several groups have tried to develop methods to predict the response to various chemotherapeutic drugs or therapeutic agent. Some of the groups analysis the tumor samples collected before the treatment and identify gene expression profiles that could be associated with response [32]. Success examples with this approach have been reported in breast cancer neo-adjuvant treatment studies and Childhood acute lymphoblastic leukemia[33, 34]. Meanwhile, others try to develop the approach to generate such profiles through identifying genes or pathways by using cancer cell lines treated with chemotherapeutic drugs in vitro. Indeed, a gene expression signature that can be used to predict the sensitivity of Src inhibitor dasatinib has been reported[35].

Pharmacogenomics is the study that examines the impact of genetic variations on the response to medications, which involves the study of changes in DNA sequence, chromosomal aberrations, and epigenetic alterations of the chromatin and DNA. This approach enables drug therapy at the most appropriate dosage for an individual patient, with the increased efficacy and safety of medications. For example, thousands of women with hormone receptor-positive breast cancer will receive tamoxifenas, but for many of them the drug has little or no effect. The ongoing research has found that women with a certain SNP in the *CYP2D6* gene have poor tamoxifen metabolism, suggesting that women may undergo *CYP2D6* genotype testing before treated with tamoxifen[36].

In addition to DNA sequence alterations, epigenetic modifications may also play a key role in the development of chemoresistance and chemosensitivity[37]. In the case of gastric cancer, BNIP3 and DAPK methylation predicts lower response rates and poor prognosis in patients treated with fluoropyrimidine-based chemotherapy[38].

Generally, with the help of gene expression signature and the advanced understanding of molecular mechanisms, personalized cancer medicine leads to more effective medical decisions, reduce probability of negative side effects, and may play an active part of the clinical trials.

3 Personalized cancer medicine in cancer prognosis

In order to eliminate any remaining cancer cells, many patients now have to receive some form of adjuvant therapy which they actually don't need. In the case of breast cancer, 85% ~ 95% of women with early-stage breast cancer undergo a toxic therapy after surgery and localized radiation treatment, but according to the meta-analyses only 20% ~ 30% of them may have recurrence, which means over half of the patients are over-treated[13]. It's clear that discovery of new prognostic biomarkers predicting the clinical outcome for a patient will dramatically improve the treatment of cancer. The approaches of personalized medicine mentioned above also contribute to disease prognosis. For example, gene expression profiles can be used to predict drug resistance as well as clinical outcomes. Such as the famous 70-genes prognosis signa-

ture strongly predicts distant metastases in breast cancer with genes regulating cell cycle, invasion, metastasis and angiogenesis[17]. The 76 - genes prognosis signature identified by another group also can be used as a powerful tool for identification of patients at high risk of distant recurrence in breast cancer[18]. These findings provide a strategy to distinguish patients who would benefit from adjuvant therapy and who would not.

Recently, GWAS identified several SNPs that modulate cancer clinical outcome, a colorectal cancer (CRC) susceptibility variant rs10795668 might be used as a biomarker to identify CRC patients with high risk of recurrence after chemotherapy[39]. Meanwhile, two functional SNPs in the important tumor suppressor gene p53 and its ubiquitin ligases MDM2 have been reported associated with poor prognosis. As p53 Arg72Pro Pro/Pro was associated with a 2 - fold increased risk of death in all esophageal cancers, whereas AMDM2 T309G G/G was associated with a 7 - fold increased risk of death in squamous cell carcinoma[40]. Besides SNPs in protein coding genes, SNPs in miRNAs may also contribute to prediction prognosis. AG >C polymorphism (rs2910164) in the miR -146a precursor sequence is associated with the risk and prognosis in adult glioma[41].

In addition, as metabolites are the end products of cellular regulatory processes, their levels reflect to genetic or environmental changes. Numerous metabolic pathways behave differently in cancer cells, especially pathways that involved in cellular growth and proliferation. Metabolic profiling using by mass spectrometry also shed light on identifying new prognostic markers and predicting therapeutic response[42]. A group has reported that a approach integrated functional genomics and metabolomics can define poor prognosis in human neuroendocrine cancers[43].

4 Challenges to personalized medicine of cancer research

Although it seems that no one would argue about the importance of personalized medicine in cancer treatment, encompassing screening, diagnosis, prognosis and prediction of therapeutic efficacy, several challenges in the clinical application of personalized medicine still have to be considered. The core concern is that cancer is a complex disease, despite the various genetic defects, environmental factors such as age, nutrition and lifestyle, can also influence disease and treatment response as well. For example, the anti-EGFR drugs panitumumab and cetuximab have been used as targeted therapy for metastatic colorectal cancer, but not all the patients with positive EGFR expression respond to the drugs, such as patients with mutations of KRAS, BRAF, PIK3CA, or inactivation of the tumor suppressor gene PTEN[44]. The increased knowledge of EGFR signaling relationships allows the development of combinative therapies to improve effective use of EGFR inhibitors in clinical practice, but many tumors remain resistant to these therapies for unknown reasons[45]. Second, although there have been a lot of advances in basic research, the translation into clinical care and improvements in patient outcomes is rare. It may take decades to study a gene's function and association to drug response. Third, quality standards for different laboratories should be established, which encompasses several aspects including the type of specimen to be analyzed, the appropriate methods of specimen collection and storage, the choice of the target genes or proteins to be tested, the platform to be used, optimal experimental conditions, and the clinical interpretations of tests[46]. As in breast cancer prognosis, by using a similar approach, both of the 76 genes assay and 70 genes assay are validated independently by other groups, but only three genes are in common in these two assays[13]. It seems that such gene expression signatures are unstable between different laboratories.

Another important concern is the higher cost of personalized medicine that will provide more detailed predictive and prognostic information about each individual patient. Setting up the infrastructure for PM will require significant spending. However, as technology advanced, such as next generation sequencing, prices are becoming much more affordable. Reduced courses of unnecessary chemotherapy or radiotherapy may also save the cost of patients[46].

5 Future prospective

Translational medicine, which is the process of turning appropriate biological discoveries into drugs and medical treatment, enables new approaches in personalized medicine from prevention to diagnosis, treatment, and prognosis to drug development. The person with high risk of a particular cancer diagnosed by genetic testing can benefit from choosing a preventive lifestyle or drug prophylaxis. The molecular classification and staging based on DNA-microarray technology helps better understanding of the characteristics of an individual tumor and developing clinically relevant tests which are likely to affect patient therapy and drug development in the future. Increased knowledge of molecular oncology has enabled the targeted therapy and may lead to a more effective treatment and fewer side effects for patients. The GWAS project and whole genome sequencing project allow the acquisitions of genetic information that can predict the risk of recurrence and clinical outcome. With the help of all

these strategies, patient may receive more effective tailored therapy that targeting the specific tumor. Although many challenges to the personalized medicine remains, there is no doubt that personalized medicine will make a new epoch in cancer therapy.

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