CHALLENGES AND PROMISES OF PHARMACOGENETICS IN CANCER THERAPEUTICS

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Abstract. Genetic constitution represents an important cause for individual variations in the response and tolerance to drug treatment. These variations are due to the germline mutations in genes that encode for drug-metabolizing enzymes, transporters, cellular targets and signaling pathways. The identification of genetic variations that predict for drug response is an important step towards the translation of pharmacogenetics into clinical practice. The knowledge of pharmacogenetics can aid in the discovery, development and individualization of anticancer drugs.

Keywords: pharmacogenetics, single nucleotide polymorphisms, messenger RNA (mRNA), pharmacogenetic tests

Introduction

The advances of molecular biology and molecular genetics and genomics, and of the associated methods and technologies, have had a major impact on our understanding of biology and drug action, and these tools are quintessential and indispensable for future progress in biomedicine and health care.

Cancer development is a multi-step process through which cells acquire increasingly abnormal proliferative and invasive behaviours. Cancer also represents a unique form of genetic disease, characterized by the accumulation of somatic mutations in a population of cells undergoing neoplastic transformation [1,2].

Pharmacogenetics describes the interactions between drug and individuals’ characteristics (which may be related to inborn traits in a larger or smaller extent).

Therefore, pharmacogenetics is based on observations of clinical efficacy and/or the safety and tolerability profile of a drug in individuals (the phenotype), and tests the hypothesis that inter-individual differences in the observed response may be associated with the presence or absence of individual-specific biological markers that could allow prediction of individual drug response. Such markers are most commonly polymorphisms at the level of the nuclear DNA, but also other types of nucleic acid-derived data, such as quantitative gene expression measurements, which serves as surrogate for the presence of underlying variants in the DNA.

It is known that two types of allelic variants

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have been described. Mutations are rare variants that are frequently associated with changes in the encoded amino acids in congenital disease. The term polymorphism is used to describe allelic variants that are detected in > 1% of a given population. The most common types of polymorphisms are single nucleotide polymorphisms, known as SNPs.

Drugs, among all the „environmental factors” that we are exposed to, may be likely to interact specifically and selectively with the genetic properties of a given individual, as their potency pitches them into a narrow “therapeutic window”, balanced between potent potions and perilous poisons.

An important distinction between pharmacogenetics in oncology and other therapeutic fields concerns somatic mutations, acquired in cancer tissues, which contribute to the variations in treatment outcome and could be exploited in targeted therapy to maximize treatment efficacy.

The application of pharmacogenetic testing in cancer therapy is attractive because of the narrow therapeutic index of chemotherapeutic agents.

The identification of candidate genes for pharmacogenetic analysis is a complex process because the activity of anticancer drugs is influenced by some factors, such as:

1. metabolic activation and inactivation (e.g., CYP450 and UGT) expression of drug targets [e.g., thymidylate synthase and epidermal growth factor receptor (EGFR)]
2. integrity of pathways that recognize the cellular damage and promote or inhibit 3. apoptosis (e.g., p53 and Bcl-2)
3. DNA repair systems (e.g., ERCC1, XPD)
4. active drug transport outside the cell (e.g., ABC transporters)

Metabolizing enzymes of the folate pathway

*Methylenetetrahydrofolate reductase and methotrexate*

Methotrexate exerts its cytotoxic effects by inhibiting several folate-dependent enzymes, such as dihydrofolate reductase, thymidylate synthase and aminoimidazole carboxamide transformylase.

5, 10-methyltetrahydrofolate reductase (MTHFR) is an important enzyme that regulates folate and homocysteine homeostasis. Deficiency in MTHFR has been associated with a reduced folate pool, as well as neurological and vascular diseases.

MTHFR677C-T variant is associated with a decreased folate level, and patients with variant MTHFR677C-T allele are more likely to experience treatment related toxicity after methotrexate, as part of the regimens for breast cancer, ovarian cancer and bone marrow transplant[16-17].

**Drug targets**

*Thymidylate synthase and antimetabolites:*

Thymidylate synthase (TYMS) catalyses the methylation of deoxyuridine monophosphate (dUMP) to deoxythymidine (dTMP), the only source of intracellular thymidylate essential for DNA replication and repair [?].

It represents the main target for 5-FU, capecitabine and raltitrexed. The overexpression of TYMS is associated with resistance to 5-FU and other TYMS inhibitors such as raltitrexed [8, 9] and reduced response to hepatic artery infusion of flouxuridine [10].

Gene amplification can result in the overexpression of TYMS. Wang et al. have demonstrated the feasibility of using fluorescence in situ hybridization to detect TYMS gene amplification in cancer tissues. The results from the study have shown that the patients with metastatic colorectal cancer, containing TYMS amplification had a poorer survival. This thing suggests that TYMS amplification is a major mechanism of 5-FU resistance [11].

**Epidermal growth factor receptor and tyrosine kinase inhibitors:**

The epidermal growth factor receptor (EGFR) is dysregulated and overexpressed in many epithelial cancers, such as non-small cell lung cancer and head and neck cancer. Because the EGFR signaling is important for the tumor cell proliferation and angiogenesis, it has become an attractive target in cancer therapy [12]. Two oral EGFR tyrosine kinase inhibitors (TKI), gefitinib and erlotinib, are used as second- and third-line therapy in advanced non-small-cell lung cancer.

Different populations showed significant variability in the response to these drugs. The response rate of gefitinib is higher in Japanese patients in comparison with Caucasians [13].

Somatic mutations in the tyrosine kinase domain of the EGFR were found to be present in most patients who responded to gefitinib and erlotinib [14]. It is supposed that these mutations, which cluster around the ATP-binding site of the tyrosine kinase domain (exons 18, 19 and 21), stabilize the interaction between drug and tyrosine kinase domain.
Within the tyrosine kinase domain, a point mutation, T790M, confers resistance to gefitinib [15].

Clinical applications of pharmacogenetic tests in cancer therapeutics

A pharmacogenetic test is a genetic test with the objective of influencing the choice of drug or dose used in the treatment of an individual patient. These kind of tests may be conducted on the person (to test for inherited variation) or on the diseased tissue (currently confined to oncology).

The conducted test would usually be an examination of the genomic sequence looking for specific variants, but it could include expression analysis, meaning a quantitative or qualitative determination of the messenger RNA transcribed in a tissue or organ.

Many studies have supported the use of pharmacogenetic testing for UGT1A1 and TPMT polymorphisms. Pharmacogenetic testing can enable doctors to identify which patients are less likely to benefit from expensive drugs, and those who are susceptible to severe treatment related toxicities at standard treatment doses, making in this way the treatments safer and more cost-effective.

Also, the availability of high-throughput genotyping platforms, has allowed for a large set of SNP markers that are studied and may lower the cost of pharmacogenetic testing.

The utility of pharmacogenetics extends beyond cancer therapy. It has the potential to facilitate the identification of drug targets and accelerate drug discovery and development.

It is known that tumor tissues acquire mutations in oncogenes, which can confer sensitivity to drugs, as is the case of EGFR tyrosine kinase domain mutation and response to gefitinib.

Incorporating of pharmacogenetic testing early in the clinical trials can provide important information regarding the pharmacogenetic profiles with treatment responses and tolerability.

Also, it is possible to identify several potential goals for clinical pharmacogenetic testing:

1. the sub-division of common diseases into different molecular sub-types, which may be more or less susceptible to specific treatments
2. developing of more logical approaches to dosage, efficacy and the prevention of adverse reactions by analyzing the genetic basis for differences in the pharmacodynamic or pharmacokinetic properties of drugs
3. identifying genetic susceptibility to various common diseases that offer targets for pharmacological intervention.

Conclusions

The pharmacogenetic testing has provided important evidence for the genetic basis of drug response and tolerability.

Despite of the extensive use of pretreatment pharmacogenetic, testing is still limited, the prospects of using pharmacogenetic testing to tailor individual therapy regimens in the future are very promising.

References

12. Mendelsohn J Targeting the epidermal growth factor re-
ceptor for cancer therapy. *J Clin Oncol* 2002; 20: 1S-13S.


