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Editorial

Cancer Pharmacogenomics

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INTRODUCTION

Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.

Somatic mutations in cancer pharmacogenomics. Somatic mutations may be the drivers that define the cancer subtype, or they may simply be passengers. Tumour samples are a mixture of cancer and normal cells, and this must be accounted for when calling somatic mutations in DNA-sequencing studies

Cancer pharmacogenetics allows identification of patients at risk for severe toxicity, or those likely to benefit from a particular treatment and thus helps us move toward the ultimate goal of individualized cancer therapy.

Candidate polymorphism search refers to finding polymorphic DNA sequences within specific genes that are candidates for certain traits. Within pharmacogenomics, this method tries to resolve pharmacokinetic or pharmacodynamic traits of a compound to a candidate polymorphism level. This type of information can contribute to selecting effective therapeutic strategies for a patient.

To understand the potential functional impact of a polymorphic DNA sequence, gene silencing can be used. Previously, siRNAs have been commonly used to suppress gene expressions, but more recently, shRNA have been suggested for use in studying and developing therapeutics.

Another new method being applied is Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR). CRISPR, combined with the Cas9 enzyme, form the basis for the technology known as CRISPR-Cas9. This system can recognize and cleave specific DNA sequences, and thus is a powerful system for gene silencing purposes.

The current treatment for most cancers includes using cytotoxic chemotherapy, which is not precisely targeted to the somatic mutations that drive malignant transformation as such driver mutations are unknown for most patients. Studies of cell line pedigrees treated with various chemotherapeutic agents have shown that some cytotoxic effects are probably heritable1–3. Variations in the toxicities and responses experienced by cancer patients have led researchers to search for germline genetic variants associated with chemotherapy-induced phenotypes. One well-described example is that the standard dose of mercaptopurine (which is a treatment for acute lymphoblastic leukaemia (ALL)) results in life-threatening toxicity for individuals with certain variant alleles of thiopurine S-methyltransferase (TPMT)4–6. The US Food and Drug Administration (FDA) now recommends genotyping of TPMT, and individuals with inactive alleles are often successfully treated with reduced doses of mercaptopurine4,7,8. Additional key germline genetic variants that are associated with cancer-drug-induced phenotypes.

Cancer pharmacogenomic studies have challenges in addition to those common to other pharmacogenomic studies. Optimizing the design at the outset of a cancer pharmacogenomics study will increase confidence in the findings, and the aim of this article is to provide information about study design and analytical options.

With new tools and technologies continuing to develop, there are growing opportunities to analyze cancer at the single-cell level. Corresponding approaches with whole-genome sequencing can also be applied to single-cell sequences and analyses. This level of pharmacogenomics has implications in personalized medicine, as single-cell RNA sequencing and genotyping can characterize subclones of the same tumour, and lead to the identification therapy-resistant cells, as well as their corresponding pathways.

As the ability to analyze and profile cancers continues to improve, so will the therapies developed to treat them. And, with increasing attention being given to whole-genome sequencing

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and single-cell sequencing, there will be a growing amount of pharmacogenomic data to analyze. These analyses will rely on new and improved bioinformatics tools to help identify targetable genes and pathways, to help select safer and more effect therapies for cancer patients.

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CONFLICT OF INTEREST

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