Personalized Cancer Management

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The aggression of cancer is characterized by its multigenic and heterogeneous nature. With the completion of the Human Genome Project in 2003, there has been growing interest in the field of personalized medicine for cancer management, using an individual's genetic composition to direct prevention, detection, prognostic, and therapeutic efforts. This review will provide an overview of some of the molecular profiling techniques that are currently in use, including transcriptomics, proteomics, and genomics using assessment of single nucleotide polymorphisms (SNPs), copy number variation (CNV) and high-throughput gene sequencing. Some recent examples of personalized medicine applications in the screening, diagnosis, tumor classification, and targeted therapy of various types of cancer will also be discussed. Although more validation and consolidation of these research studies is required before personalized medicine is widely used for cancer management, its potential benefits hold implications for pharmaceutical companies, diagnostic agencies, healthcare providers, and most importantly, patients.

Introduction

A diagnosis of 'cancer' is a life-changing event for patients. An estimate of over 10 million people globally will die annually as a result of cancer in the year 2020. It is not surprising that there is a drive to further our understanding of the disease mechanisms, pathophysiology, and treatment of cancer. The multigenic and heterogeneous nature of cancer has long been recognized, and this heterogeneity can determine the aggressiveness of cancer in an individual patient. The completion of the Human Genome Project in 2003 has brought forth the hope of advancing medical practice into a “genomic era” that will identify key therapeutic targets and disease biomarkers for cancer. Despite these advancements, much of the systemic therapy for cancer patients is still empirical and two patients who may be at apparently 'identical' stages of cancer and harbor the 'same' tumor type will exhibit significantly different clinical outcomes as measured by survival and therapy response.

Instead of continuing to progress down the traditional ‘trial and error’ method of testing for new therapeutic agents, the personalized medicine model has been proposed because of its theoretical appeal: in this model, an individual's genetic composition helps focus and direct prevention, detection, prognostic, and therapeutic efforts. This article will provide an overview of the current status of molecular profiling technologies and their current applications in personalized medicine, from the initial stages of identifying significant causative and modulating genes to the integration of multiple genes within a personalized profile that will direct therapy in the sub-population of cancer patients.

Molecular Profiling Techniques

The main molecular platforms currently widely used in personalized medicine are transcriptomics, proteomics and genomics, which includes the analysis of single nucleotide polymorphisms (SNPs), copy number variations (CNVs) and high-throughput gene sequencing. Of course, these are often not mutually exclusive and one of the current goals in personalized medicine is to develop an approach to utilize and integrate the information from different techniques.
Transcriptomics, the study of altered expression of the levels of messenger RNA (mRNA) within cancer tissue samples or biopsies, has led to the development of Internet-based resources such as Oncomine Research Platform that maintains a catalogue of published transcriptome profiles so that clinicians and scientists can easily access the information. Although microarray technology, the main means of transcriptome profiling, is cost-effective and accurate, it is still inhibited by sample heterogeneity and the absence of a high-quality multi-institutional tumor tissue library that would be necessary to cater to a large population.

Proteomics also explores genetic expression, but at the level of translated protein quantity, structure and function within cancer tissue samples. While technically more difficult than transcription profiling, proteomic analysis has the advantage of more directly examining molecular machinery of cell physiology, post-translational modifications, and protein-protein complexes. Mass spectrometry and protein microarrays have also been used to target specific biomarkers in signaling cascades, although there are some limitations with respect to difficulties in large-scale target identification as the exact number of polypeptides produced is still uncertain.

Finally, there is a wide range of genomic DNA variations that predispose or propagate the development of cancer. Examples include single nucleotide polymorphisms (SNPs), which are genetic variations in the DNA sequence due to the difference of one nucleotide among individuals. Copy number variations (CNVs) refer to larger-scale changes, including gene duplication, deletion, inversion or translocation events. Both SNPs and CNVs have been linked to a wide range of different physiological phenotypes and diseases. However, this is only an initial step; the examination of genomic DNA in a patient’s germline or in somatic cells taken from cancerous tissue can stratify risk and identify new causative genes and pathways, but this information alone is not sufficient to define mechanisms of disease or therapeutic approaches.

The ultimate genomic assessment is whole-genome sequence analysis, in which all 3 billion nucleotides of genomic DNA from an individual patient or the cancer tissue sample are analyzed using automated nucleotide sequencers to determine potential functional changes from a normal reference sequence. There have been many initiatives such as the Human Cancer Genome Project and Cancer Genome Anatomy Project to use high throughput gene sequencing to identify novel disease-associated mutations at a genome-wide level. Much of the attention has shifted from mastering the technologies themselves to extracting biologically relevant information – a field called “bioinformatics” - such as pairing screen results with functional assessments of a specific neoplastic process. Despite the more comprehensive sequence information at the expense of a higher cost, there have been some applications of genomic and bioinformatic analysis in tumor classification.

Screening and Diagnostics

Preventive measures taken against cancer can use personalized medicine to screen for one's predisposition to cancer, which is important in providing a wider range of therapeutic options for the patient and guiding in clinical decision making. Genetic screening is particularly useful for individuals with a family history of cancer, where the presence of oncogenic mutations such as APC (adenomatous polyposis coli), BRCA1 (breast cancer 1, early onset), and BRCA2 (breast cancer 2, early onset) can be used as risk factors before any symptoms or even cellular dysplasia occurs. Celecoxib, the current chemopreventive agent of choice for colorectal cancer, is only recommended for high-risk patients with familial adenomatous polyposis linked to the APC oncogene mutation. There is also a drive to utilize personalized medicine in clinical diagnostics. Although the prostate-specific antigen (PSA) is the gold-standard for detecting prostate cancer, greater diagnostic accuracy in unscreened populations can be achieved if biologically-based prediction models are used to link biomarker levels to other individual factors such as age.
Prognosis and Tumor Classification

Another important goal in personalized medicine is to consolidate information from traditional prognostic factors and genetic profiles in order to optimize treatment for patients. An important prognostic biomarker for breast cancer is the human epidermal growth factor receptor 2 (Her2), which encodes a transmembrane receptor protein that is overexpressed in breast cancer cells. Specifically, these levels can be used to predict clinical outcomes; serial changes in the circulating Her2 extracellular domain (ECD) levels have paralleled the clinical course of disease regardless of the treatment. Specifically, higher ECD levels have been correlated with earlier recurrence of breast cancer. There is also a 186-gene “invasiveness” gene signature (IGS) generated from differentially expressed genes that has been found to be strongly associated with metastasis-free survival and overall survival of medulloblastoma, lung cancer, prostate cancer, and especially breast cancer. Hence, bioinformatics-centric prediction models have been gaining ground in predicting the therapeutic response of common tumors based on their gene expression profiles.

Targeted Therapy

Current research has been progressing towards a consolidation of our current knowledge on diseases, genetic alterations, and drug responses, allowing both the creation of new chemotherapeutic drugs and expanding existing ones on the market. For instance, imatinib meyslate (Gleevec) is a drug that was initially approved by the Food and Drug Administration in 2001 to treat chronic myelogenous leukemia (CML) by targeting the BCR-ABL protein. Later, Gleevec became the first specific effective treatment against advanced gastrointestinal stromal tumors (GISTs) after researchers found that the link between the mutant KIT protein, which shows similarities to the BCR-ABL protein, and GIST aggression. However, researchers are still looking into ways to probe into individual resistance mechanisms to combat the issue of Gleevec resistance in patients. Gefitinib (Iressa) is another anticancer drug that targets the epidermal growth factor receptor (EGFR), an important component leading to lung cancer aggression. The concept of personalized medicine may explain why there were largely negative results of clinical trials as only 10-15% of the test patient population carried the EGFR gene mutation or gene amplification. Hence, clinicians are looking into the possibility of conducting more targeted trials that restrict eligibility of subjects to those whose molecular profile predicts a better response to a particular chemotherapeutic agent.

Challenges and the Future of Personalized Medicine

Although there is much hope regarding the potential of personalized medicine, there are still many barriers preventing its widespread usage. Duffy et al. illustrate some of the key challenges in the field, including underpowered studies, invalidated results from independent patient populations or prospective trials, multiple end points and subsets of patients used, and poor quality of design and unreliable data. These problems can be addressed in part by better coordinated multi-centered prospective studies using much larger patient cohorts than have been studied to this point. Nonetheless, the potential benefits of personalized medicine – with respect to improving positive outcomes and minimizing side effects and costs of treatment - are worth taking the time and effort to pursue. This holds implications for pharmaceutical companies, diagnostic agencies, members of the healthcare profession, and most importantly, patients. Indeed, there is a movement towards focus on the individual and not just the disease—what has been a barrier to treatment in the past may very well be the key to unlocking mechanisms of disease to combat cancer in the future.

References

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