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Translational Approaches and Challenges for Personalized Cancer Medicine

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Abstract—*Since the Human Genome Project, the emerging scientific era of "omics" has revolutionized the study of cancer. Cancer is driven fundamentally by genetic changes in a multistep progression still being understood, even in the most studied cancer types. Cancer Genome Consortia are coordinating efforts aimed at identifying all genomic alterations significantly associated with cancer, including genomic loss or amplification, mutations in coding regions, chromosomal rearrangements, aberrant methylation, and expression profiles. The discovery stage targets the decoding of cancer genomes and using the knowledge for Personalized Cancer Medicine. This study also highlights technologies that empowers cancer genomics, compares sequenced genomes, identifies challenges in the discovery of new genetic aberrations and discusses the translation of study of cancer genomics to applications in the clinic.*

1. INTRODUCTION

Research in the area of cancer genomics has gained momentum with the reduction in the cost of sequencing and advancement of technologies that lead to more in-depth and accurate interpretation of sequenced data. The rate of errors associated with sequencing and genotyping have dropped dramatically with the new technologies. The measurement of genetic alterations leading to cancer, for diagnostic understanding as novel biomarkers and for discovery of new drugs based on consistentt alterations, is being studies by many scientists all over the world for a foray into the era of personalised cancer medicine. The Cancer Genome Atlas and the International Cancer Genome Consortium provide the reservoir of information for characterizing dozens of cancers and large scale data mining for understanding the differences between normal and tumor variants. The Cancer Genome Atlas has generated genomic datasets with genomic insights for over 20 malignancies. Interlinking and understanding the clinical phenotype and the genomic data genrated by either consortia poses a major challenge.

2. ALTERATIONS IN CANCER GENE SEQUENCE

The central aim of cancer research is identifying the alterations in mutated genes that have been known to cause cancer. So far 291 genes have been reported to cause cancer which makes about 1% of the human genes. 90% of these genes show somatic mutations, 20% show germline mutations and 10% show both (1). More than 1000 somatic mutations have been found in 274 mega bases of DNA corresponding to the coding exons of 518 protein kinase genes in 210 diverse human cancers (2). The first report of a somatic mutation in a human cancer gene was the conversion of amino-acid 12 of HRAS from glycine to valine in the human bladder carcinoma cell line T24/EJ1. It is likely that most somatic mutations do not confer a clonal growth advantage. So, cancer genomes carry several 'PASSENGER' mutations. Interpreting a gene change to be the reason for cancer development is based on rationale and cannot be attributable to chance. In cancer cells having high prevalence of somatic mutations, it is difficult to ascertain which mutations have played a role in causing cancer. In mutations like mismatch repair gene defects that carry thousands of small insertions and deletions in short tendem repeats, they are mostly found to be in intergenic or intronic regions and most certainly come under the category of passenger mutations. Following types of mutations have been included in cancer gene census (1):

- Base substitutions that lead to missense amino-acid changes, nonsense changes and alterations in the well-conserved positions of splice sites.
- Insertions or deletions in coding sequences or splice sites that might cause in-frame or frameshifting alterations in the protein.
- Rearrangements because of chromosomal translocations that lead to chimeric transcripts or to deregulation of genes through apposition to novel promoter or enhancer regions.
- Copy-number increases and decreases.

Most classes of mutations (such as base substitutions) only affect a single gene, or, at most, two genes (such as reciprocal chromosomal translocations). However, copy-number changes, such as gene amplification, can affect several megabases of DNA and encompass many genes. Solely on the

basis of genetic evidence, it is not always clear which gene is the crucial target of the amplification, and it is conceivable that, in some cases, there is more than one target. Chromosome defects, such as trisomy, that involve even larger regions of the genome pose even greater problems, as they might alter the copy number of thousands of genes .

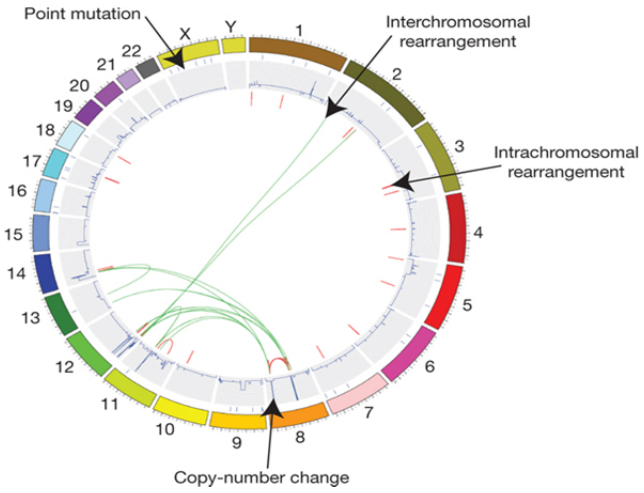

Fig. 1: The Cancer Genome (3) (Individual chromosomes are in outer circle, Concentric tracks for point mutation, copy number and rearrangement data relative to mapping position in the genome, Arrows indicate examples of the various types of somatic mutation present in this cancer genome)

3. PERSONALIZED MEDICINE

Personalized medicine is referred to as the ability to segment heterogeneous subsets of patients whose response to a therapeutic intervention within each subset is homogeneous. (4) The key to success in personalized medicine is to uncover molecular biomarkers that drive individual variability in clinical outcomes or drug responses (5). Not all patients respond equally to cancer therapeutic compounds. With the latest techologies like high-throughput genomic, transcriptomic, and proteomic type along with enhanced understanding of the molecular mechanisms of cancers allow uncovering genes that show individual variations in clinical outcomes or drug responses.

Traditional medicine that is prescribed for all cases of a particular diseaseas promotes the risks of drug toxicities and treatment failures (6). The ultimate goal of personalized medicine is to furnish the proper treatment to the right person at the right time (7). The impact of personalized medicine will depend on discovery of novel biomarkers that will diagnose and direct personalised treatment for a particular cancer. According to the U.S. National Institutes of Health (NIH), personalized medicine is "an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease" (8). The U.S. Food and Drug Administration defined personalized medicine as "the best medical outcomes by choosing treatments that work well with a person's genomic profile or with certain characteristics in the person's blood proteins or cell surface proteins"(9).

Personalized medicine integrates personal genetic or protein profiles to strengthen healthcare at a more personalized level, particularly with the aid of recently emerging "omic" technologies such as nutritional genomics, pharmacogenomics, proteomics, and metabolomics [95].

Personalized medicine develops safe and effective treatments by targetting specific regions altered in an individual (7). In fact, genetic biomarkers are the foundation of personalized medicine as they are associated with a particular disease. Knowledge of a patient's genetic profile leads to the proper medication or therapy so that physicians can manage a patient's disease or predisposition towards it using the proper dose or treatment regimen (8). Diagnosis that is individual specific can lead to early intervention and hence be very useful as in the example of females with genetic mutations in the *BRCA1* or *BRCA2* genes which have a higher chance of developing breast cancer compared to those in the general female population (10, 11). An accurate test of these breast cancer susceptibility genes can guide surveillance and preventive treatment based on objective risk measurements such as increased frequency of mammography, prophylactic surgery, and chemoprevention. (12). Personalized medicine enables physicians to select optimal therapies and avoid adverse drug reactions. Molecular diagnostic devices using predictive biomarkers provide valuable information regarding genetically defined subgroups of patients who would benefit from a specific therapy (7).

4. TECHNOLOGIES AIDING PERSONALISED MEDICINE

Due to revolutionary advances in DNA sequencing techniques, the field of cancer genomics is growing rapidly. The recent technology developments which aids in more understanding of cancer biology are whole genome sequencing (WGS), targeted sequencing, genotyping and bioinformatics. Next generation sequencing techniques have also created significant advances in the road to personalised medicine. Reduction in cost of sequencing and advancement in technologies are encouraging more cancer sequencing projects. Due to the same reason, the list of genes of interest is expanding continuously and identification, validation and functional investigation of genetic mutations are being pursued. Bioinformatics and stringent quality control have dropped the rate of errors associated with sequencing and genotyping, the reliability and accuracy of novel technologies remain potential problems. Although compatible treatments to novel biomarkers is the crux of personalised cancer medicine, key challenges associated with tissue processing and tumor heterogeneity must be recognized and addressed (14).

5. PERSONALIZED CANCER MEDICINE

The way of getting personalized cancer therapy is getting feasible because of tremendous increase in understanding of molecular oncology, developing novel therapeutics and affordable next generation sequencing. However, patient's germline DNA along with the molecular characterization of the tumor is to be interpreted by the clinician to implement genomically informed therapy. Therapeutic implications of genomic modifications like mutations, insertions/deletions, fusions and copy number changes are the common genomic alterations which need to be curated since it is believed that they affect the function of a cancer gene. Those alterations are actionable which can be targated either directly or indirectly with approved therapies. Biomarker-based therapy in routine clinical practice is not possible due to either the clinical data for such genomic alterations is absent or insufficient. A frequently updated knowledge base which describe genomic changes and their clinical implications is a need of time today which will also help in continued education of clinicians and patients. Genomically informed therapy is now a reality and that is because of emergence of molecularly targeted therapies. Other than somatic alterations there are two more ways of genomic alterations i.e. epigenetic regulation and RNA editing. (13)

6. BIOMARKERS IN CANCER DIAGNOSTICS AND MEDICINE

A biomarker is a a normal biological process, a pathogenic process, or a pharmacological response to a therapeutic intervention (15). Biomarkers include physiological measurements, molecular (DNA, protein, metabolite) or cellular measures from biofluids (blood, plasma, serum, and urine), molecular, cellular or histopathological measures from solid tissue samples, and measurements from magnetic resonance imaging or computed tomography images (16). A prognostic biomarker is related with a patient's clinical outcome and can be used to select patients for an adjuvant systemic treatment irrespective of the patient response to treatment, whereas a predictive biomarker is related to the patient's response to a particular intervention (17). A prognostic biomarker provides information about the patients overall cancer outcome irrespective of the therapeutic response (18). Treatment for breast cancer based on such markers will be mostly on parameters like nodal status, tumor size, tumor type/grade, lymphatic and vascular invasion, tumor hormone receptor, age, and ethnicity. Prognostic biomarkers that provide better information on relapse risk could prevent many patients from chemotherapy toxicity without compromising survival (19).

A predictive biomarker provides information about the effect of a therapeutic intervention (19). In other words, a predictive biomarker enables screening of a subset of patients that are responsive to a specific therapy where response is defined by any of the clinical endpoints commonly measured in clinical trials (20). As a predictive biomarker indicates heterogeneous benefits contingent upon sub-patient risk groups classified by the status of the biomarker, a significant interaction between treatment effects and patient categories needs to be statistically validated, ideally in a randomized clinical trial (21). Predictive biomarkers can help physicians to forecast the effects of a particular treatment. Numerous proteins and genes exist that are specifically associated with breast cancer growth, proliferation, and metastasis. The deeper understanding of their roles regarding the responses of various therapies may empower physicians to determine optimal treatments for patients with breast cancer (22).

Personalized cancer medicine integrates personal genetic or protein profiles to strengthen healthcare at a more personalized level, particularly with the aid of recently emerging "-omic" technologies such as nutritional genomics, pharmacogenomics, proteomics, and metabolomics (23). Knowledge of a patient's genetic profile leads to the proper medication or therapy so that physicians can manage a patient's disease or predisposition towards it using the proper dose or treatment regimen. An accurate test of these breast cancer susceptibility genes can guide surveillance and preventive treatment based on objective risk measurements such as increased frequency of mammography, prophylactic surgery, and chemoprevention (24).

7. CLINICAL OUTCOMES AND DRUG RESPONSE

The critical component to success in personalized medicine is to uncover gene signatures that drive individual variability in clinical outcomes or drug responses. A number of approaches have been proposed to identify predictors for patient prognosis and response to cancer treatments.

Data driven approach- Biomarkers associated with tumor traits are objectively searched in genome-wide analysis using data-mining tools. The merit of this approach is an unbiased biomarker discovery. However, such an approach is difficult to validate by the data-driven approach as they are difficult to interpret due to limited knowledge about their biological functions.

Knowledge driven approach- Selecting candidate genes using prior knowledge or surveying the literature for evidence of linkage to either cancer pathological processes or pathways important in drug responses may be included in this approach. However, genes generally unknown to be involved in a process cannot be included in this approach..

The combination of the data-driven and knowledge-driven approach has been used to develop gene signatures [25]. Biomarker discovery in genome-wide analysis has a drawback that there are far more genomic variables than the number of samples [26]. The use of knowledge-driven approach to reduce the number of candidate genes detected by genome-wide search is one way to overcome this drawback.

Biomarker discovery is started by collecting molecular data in a drug response experiment in which high-throughput technologies are used to determine genomic or genetic characteristics on cell-lines. This is followed by quality control or pre-processing. High-throughput technologies introduce a lot of non- biologic noise and biases during data collection, hence normalization is required for further analysis that helps identify the subset of genes that are candidate predictors highly associated with drug activities. This step reduces the number of gene variables significantly (27). Several statistical approaches are used that rely on underlying assumptions such as distributional specifications, exchangeability for a random-effect distribution, constant coefficients of variation, a mean-variance relationship, and others. Upon narrowing down candidate genes to a few hundred, a statistical classification modeling technique is then used to construct a multivariate prediction model. However, a single biomarker is less likely to furnish sufficient sensitivity and specificity for most predictions (22). A conclusive evidence of the usefulness of a prediction model is through validation in a clinical trial (28). After refinement and validation in independent cohorts, assays can be developed that accurately predict prognosis and responses to chemotherapeutic agents, contributing to the development of "personalized medicine" for patients with cancer.

For further analysis, few breast and cervical cancer genes have been taken for prediction of biomarkers for diagnosis as well as drug therapy.

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