Pharmacogenetics in Cancer Treatment: Challenges and Recent Trends

19

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19.1 Introduction

Cancer is a genetic disorder of the genome caused by different types of genetic mutations that change the behavior of cells. The research of genomic and post-genomic analysis has provided insight into the molecular level of cancer progression. The sequencing technologies have improved the analysis of cancer genomes in first-time determination. Genome sequence of thousands of patients showed the discrete sets of potential gene alterations among patients with the same cancer tissue type. The single-cell sequencing disclosed the heterogeneity within the subclones of single tumors during evolution. Identification and characterization of these mutations and their assorted variety are crucial for treatments. Next-generation sequencing (NGS) has also been used for study of epigenomes and transcriptomes of cancer providing a comprehensive understanding of cancer pathology. This method gives an inclusive bench-to-bedside overview of cancer genomics, beneficial to researchers and clinicians alike. Available researches show that cancer genomics has improved the cancer prognosis leading toward the potential future therapeutic.

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19.2 Cancer and Genomics

Methodological achievements have revolutionized transcriptome profiling during recent decades. The RNA-sequencing (RNA-seq) made it possible to sequence and quantify the transcriptional profiles of cells. These transcriptomes show a linkage between cellular phenotypes and their molecular groundworks, the mutations. In the context of tumor, this link shows a prospect to reveal the complexity and heterogeneity of cancers and also expose the implications of new diagnostic biomarkers or therapeutic procedures [1].

Tissue morphology and risk assessment through clinical data standards help in the classification and identification of brain tumors. Modernization in genomics and epigenomics recently accompanied an epoch of describing cancers relying on molecular basis. These techniques have developed accuracy for recognizing oncogenic-driving events which eventually increased accuracy in clinical result. Brain cancer spreads through situation of inherited tendency syndromes like Li-Fraumeni or Gorlin syndrome. However, it commonly arises from attainment of somatic mutations and chromosomal variations in tumor cells. From the study of various cancer pathways, certain refrains arise and serve like drivers of cancer. These include DNA harm reparation, genomic variability, mechanical target of rapamycin path, sonic hedgehog way, hypoxia, and epigenetic dysfunction. Consideration of these pathways is vital in developing targeted therapies and recognizing the correct patients with right therapies [2].

The TC-induced macrophages tempted IL-32 translation in TC cells within which TAM- derivative TNFα was the driver of IL-32β expression in TC cells. The overproduction of IL-32β and IL-32γ cannot induce TC cell immigration but amplified the cell death. Higher expression of IL-32β promotes more transcription of the pro-survival cytokine IL-8. TAM-derived TNFα induced IL-32β in TC cells. However, IL-32β is not responsible for TC cell movement, alternate merging of IL-32 to the IL-32β isoform responsible for TC cell existence by inducing pro-survival cytokine IL-8 [2].

Quantitative next-generation sequencing shows increasing buildup of microsatellite variability between paired endometrial and atypical hyperplasia/endometrial intraepithelial neoplasia. Tumor mutations were much greater in endometrial carcinoma than in paired atypical hyperplasia/endometrial intraepithelial neoplasia specimens. This tumor mutational burden was significantly related to percent unstable microsatellite loci. Endometrial carcinoma and paired atypical hyperplasia/endometrial intraepithelial neoplasia specimens showed a progressive accumulation of unstable microsatellite loci after loss of mismatch repair protein expression. Comprehensive next-generation sequencing-based testing of endometrial carcinomas offers new insights into endometrial carcinogenesis and opportunities for improved tumor surveillance, diagnosis, and management [3].

Prominin (PROM1) and PROM2 expression differentially modifies clinical prognosis of cancer. The relationship between mutations and copy number variations in prominin genes and several types of cancers has been reported earlier. The genes that correlated PROM1 and PROM2 in certain cancers were based on their

expression levels. Gene ontology and pathway analyses have been utilized to assess the effect of these correlated genes on various cancers. It was found that PROM1 was often overexpressed in esophageal, liver, and ovarian cancers which is negatively associated with prognosis, while PROM2 overexpression was related with poor total survival in lung and ovarian cancers. Owing to characteristics of prominins, it can be concluded that PROM1 and PROM2 expression differentially modulates the clinical outcomes of cancers [4].

19.3 Drug Resistance and Cancer

Cancer possesses the ability to attain resistance against traditional treatments. The growing occurrence of drug-resilient tumor requires more research and therapies. The mechanisms that prompt the drug resistance, namely, drug deactivation, drug target modification, drug efflux, reparation of damaged DNA, reverse of cell death, and epithelial-mesenchymal transition as well as how inherent tumor cell heterogeneity, also promote drug resistance. The epigenetic modifications cause drug resistance that promote the development of cancer progenitor cells which cannot be killed by conventional cancer therapies. The most probable treatment for current drug resistance in cancer is to stop the development of cancer progenitor cells [5].

Anticancer drug resistance is an intricate phenomenon developed by altering drug goals. Developments in DNA microarray, proteomics, and targeted treatments offer novel plans to avoid the drug resistance. The resistance of cancer cell toward anticancerous agents could be made by several aspects like personal individual's genetic variances particularly in cancer somatic cells. Such resistance might be acquired by different processes such as cell death inhibition, multidrug resistance, difference in the drug digestion, epigenetic and drug goals, increasing maintenance of DNA, and gene multiplication [6].

The anticancer agents were involved significantly in the development of sterile existence and excellence of life in tumor patients. But, in several cases, after promising initial response to treatment, cancer reappearance happens. This acquired resistance to therapy is a problem for the efficiency of cancer therapy. It is a type of inherent resistance in which proteins of membrane-linking transports are involved in fundamental drug fight by varying drug carriage and its propelling out from cancer cells. Further, the steady attainment of specific genetic and epigenetic mutations in tumor cells can enhance the acquired drug resistance. The clinical data shows that the problematic nature of anti-drug property appears with an undesirable effect on molecularly targeted anticancer drugs. The medical experts suggest the recognition of such resistance mechanisms and designing the new drugs which can remove this complicacy [7].

Several features and limits must be considered as real tumor treatment using antineoplastic drugs. The way of drug management and the greatest tolerated dose can finish cancer cells while minimizing it can result in adverse effects [8, 9]. The "maximum tolerable dose" or "maximum tolerated dose" (MTD) is good known as the maximum sole dose of an agent or therapy that does not cause significant or

intolerable/opposing effects. For several drugs, the optimum dose does not essentially overlap with the MTD revealing a potency of the optimal dose stances a great challenge [10].

19.4 Cancer Genomics and Personalized Medicines

Personalized medicine practices traditional and is developing ideas of the hereditary and external foundation of ailment to modify anticipation, analysis, and action. Adapted genomics has a dynamic part without limitation, in up-to-date model of personalized medicine. The differences between genomics and genetic medicine are extra quantitative than qualitative. Ideologies developed by genomics and genetics features of medicine comprise the practice of variations as indicators for diagnosis, forecast, anticipation, targets for treatment, and clinically authenticated alternatives which are not functionally categorized. The separation of these alternatives in Mendelian and non-Mendelian factors, epigenitic charcters and the dependency on sign for medical helpfulness have serious impacts on social science. In this present change from examination to exercise, customers should be saved from problems of early version investigation outputs and encourage the advanced and profitable application of these genomic findings that raise the adapted medicinal repair [11].

High-throughput, data-intensive biomedical research assays and technologies have created a need for researchers to develop strategies for analyzing, integrating, and interpreting the massive amounts of data they generate. Although a variety of statistical methods have been designed to accommodate "big data," experiences with the use of artificial intelligence (AI) techniques suggest that they might be particularly appropriate. In addition, the results of the application of these assays reveal a great heterogeneity in the pathophysiologic factors and processes that contribute to disease, suggesting that there is a need to tailor, or "personalize," medicines to the nuanced and often unique features possessed by each patient. Given how important data-intensive assays are to show proper intervention targets and strategies for treating an individual with a disease, AI can show a significant role for personalized medicines development. We describe many areas where AI can play such a role and argue that AI's ability to advance personalized medicine will depend critically not only on the refinement of relevant assays but also on ways of storing, aggregating, accessing, and ultimately integrating the data they produce. We also point out the limitations of many AI techniques in developing personalized medicines as well as consider areas for further research [12].

Variable quantity of drug can be generated by 3D printing skill with instant release tablets, pulsatile release pills, and transdermal dose types. The 3D printing skill would be discovered positively to make modified medicines that can show a dynamic part for deadly illnesses treatment. The 3D printing-based personalized drug delivery scheme can also be examined in chemotherapy of cancer patients with value of the reduction in side effects [13].

A single human physique is a place of above 1 trillion microorganisms with a diversity of commensal microbes which carry out vital roles for health. These

microorganisms exist in various places including oral cavity, skin, gut, etc. These microbes vary in types and abundance in different organs; also these can vary among people. The genetic makeup of these microbes and their bionetwork establish a microbiome. Different features such as diet, environment, host genetics, etc. determine this wide microbial biodiversity. Experiments on human microbiome revealed a diverse microbiota between fit and unhealthy ones. This change in microbiome is due to the increased expression of genes that bring about composite ailments like cancer. Changes in microbiome may be caused by probiotics or synbiotics, diet or prebiotics. Modern sequence of genome and analysis of metagenomic deliver us the wider understanding of these probiotics with their distinctive features of microbiome in healthy and disease conditions. Molecular pathological epidemiology is helpful in providing understandings of pathological phenomena of ailment arousal and movement by defining the specific etiological features. Novel strategies target the microbial genome for therapeutic drives by which adapted medicines can be generated for curing numerous types of cancers. Screening programs can support in identifying patients about to gain cancer and in delivering appropriate approaches according to individual risk modes so that disease could be ceased [14].

19.5 Future of Pharmacogenomics in Cancer

The present pharmacogenetic methodologies face many hindrances. Candidate gene-based methodologies don't give a solid analysis of typical tissue danger and effects of drugs on tumor due to incomplete understanding of each risk factor involved in carcinogenesis. Genome-wide association study gives a progressively vigorous stage to pharmacogenetic examination as has been reported by Watters et al. [15]. These practices have different issues in clinical settings, for example, quality control which is expected due to phenotypic heterogeneity; lengthy duration involved in validation of pharmacogenetic markers; choice of the most suitable board of SNPs; investigation of the connection between genotypes, enzyme action, and gene expression; criteria for hazard appraisal and limits; and thought of ethnic varieties as the circulation and recurrence of SNPs change among various ethnic groups which makes it hard to extrapolate the discoveries of one group on another [16]. More up-to-date targeted treatments are likewise picking up fame. Trastuzumab (Herceptin), a refined recombinant monoclonal immunizer (IgG), targets HER2 (human epidermal growth factor receptor 2); Avastin (bevacizumab) represses the tyrosine kinase activity of the epidermal growth factor receptor, the expansion of which to standard chemotherapy regimens has demonstrated improved survival rates and response reaction in the treatment of metastatic colorectal malignant growth [17]. In similar manner, Erbitux (cetuximab), a monoclonal antibody, focusing on EGFR has likewise indicated promising outcomes in neck and head cancers and colorectal malignancy.

Future advancements in some key territories will assume a basic job in choosing the general impact of pharmacogenetic information on therapeutic decisions. More research is required in genome-based technologies, such as high-throughput

innovations and improvement of gene expression arrays and genome-wide outputs which could distinguish already unidentified SNPs and SNP chips and functionally significant candidate genes. Mouse models could be used for genome-wide scans in progeny from phenotypically particular mice from vulnerable and resistant strains. Transgenic and knockout approaches could likewise be utilized for setting up the key components that helps in drug response.

Candidate gene methods could be improved by consolidating a metabolic pathway approach and by information picked up from genome-wide procedures. The expense of genomic innovation (SNP) should be less expensive. For incorporation of a genetic test into clinical practice, it must give dependable, prescient, and significant data that would have generally been obscure [18]. Prior to clinical usage, solid proof from randomized controlled clinical trials is required.

During shifting toward clinical practice, validation and replication of pharmacogenomic characteristics raise difficulties. It is often hard to portray, consistently treat, and efficiently assess patients to impartially measure the medication reaction phenotype. The standard of consideration ought to be to get genomic DNA from all patients went into clinical medication preliminaries, alongside proper consent to allow pharmacogenetic studies. This is currently practiced in most huge preliminaries being led by pharmaceutical organizations and is normal for a portion of the NCI clinical trials gatherings [19–21], yet has not turned out to be standard for foundation supported or academic trials.

The main challenge for future application is the proper use of new data and the need to guarantee that following up on a pharmacogenomic marker is to the greatest advantage of the patient. The dependence on forthcoming, randomized, controlled trials as the best way to legitimize clinical implementation isn't useful and ensures that new data will have a 5- to 10-year lag, while studies are developed, led, and translated. There is likewise a separation between the funding bodies and the prioritization of this kind of study, regarding budgetary duty, clinical trial framework, and capacity to quickly sanction new techniques. There have been a few endeavors to create approaches to pick up trust in early appropriation of pharmacogenomic information, based on agreement working among establishments around the use of genetic data to medicate treatment. One such exertion is the Clinical Pharmacogenetics Implementation Consortium (CPIC), which incorporates members from >80 institutions crosswise over 4 continents [22]. There is a need to devise a structure whereby any source of variation in a clinically credentialed pathway can be advanced toward clinical execution.

The time has come to be increasingly practical as we move ahead. Although significant advancement has been made in recognizing and describing pharmacogenomic phenomena, interpretation of this information into viable clinical application remains moderate. A variety of components add to this issue, including an absence of clearness on the measure of information expected to demonstrate clinical utility, the scarcity of interventional pharmacogenetic ponders, and uncertain practical consideration, for example, how to build up and execute clear rules in departments that oversee malignancy. There are additionally societal components having an effect on everything, including acknowledgment of across-the-board

genetic testing just as suggestions for protection inclusion and risk. These issues should be investigated and tended to before the promise of genetically tweaked medication can turn into a reality.

Meanwhile we risk that crucial inventions of anticancer pharmacogenomic might not arise from growing the sample size of medical pharmacogenomic data. This is based upon insight information and revolutions of other disciplines such as medicine discoveries or designing of novel anticancerous drugs and guidelines of drug mixtures [23, 24]. Response of cancer patients follows a very heterogeneous pattern. Inherited differences of interindividual drug deposition and their effects can determine the goal of choosing the optimal drug for each patient. Cancer therapies are very significant in terms of pharmacogenetics as it shows severe toxicity and efficiency. Genetic polymorphism of genes accounts for metabolic enzymes and cellular targets for cancer chemotherapeutic agents from which the consequence chemotherapy is not possible. This particular genetic determination of drug response can transform the utility of medications. Determination of severe toxicity can help treatment leading to individualized cancer therapy for cancer patients. Guessing the cancer treatment outcome from gene polymorphism is now possible for many types of chemotherapy agents. But further research is needed from larger cancer populations along with validated pharmacogenetic markers prior to application in diagnostics [25].

19.6 Conclusion

Cancer is a heterogeneous ailment with distinctive phenotypic and genomic features that differ between individual patients and even among individual tumor regions. It is concluded that for efficient cancer therapies, characterization and identification of genomic mutations and their diversity are vital. So, linking cancer genomics with pharmacological factors is the only way to develop potent cancer therapies. For this modern technologies including next-generation sequencing, candidate gene-based analysis, etc. can play an important role in cancer therapeutics. Novel strategies target the microbial genome for therapeutic drives by which adapted medicines can be generated for curing numerous types of cancers. Future advancements in some key territories will assume a basic job in choosing the general impact of pharmacogenetic information on therapeutic decisions. The main challenge for future application is proper utilization of new data and the need to guarantee that there is strong information supporting that following up on a pharmacogenomic marker is to the greatest advantage of the patient.

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