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Review Article

Cancer Genetics: Comprehensive Analysis of Genetic Variants and Molecular Biomarkers Associated with Cancer Progression and Patient Survival

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Abstract

The development and expansion of cancer are mainly due to heterogeneous genetic structures caused by somatic mutations and several epigenetic changes. here, the expansion and development of the tumor cell and at the same time how long the metastatic artis and cancer patients can survive and at the same time the molecular markers that determine this are seriously evaluated. In addition, the transformation of malignant cells and the basic changes that occur in oncogenes and cells, as well as indels and point mutations, are discussed in a broad way. One of the researched areas is the effect of polymorphism on cancer cells and their treatment, its instability, mutational burden, and transcriptomic expressions; and the use of biomarkers for various purposes, such as prognostic and predictive purposes, is mainly investigated. In addition, many studies- next-generation sequencing, finding biomarkers of genome association studies, and new changes in the identification of genes up to the molecular level are also included. In order to improve the treatment results of cancer patients and to optimize the treatment, the correlation of multi-omic data with medical information is widely used.

Keywords: cancer genetics, germline variants, tumor progression, patient survival, molecular biomarkers, somatic mutations.

1. Introduction

Cancer is considered a very dangerous disease that has caused the death of many people in the world, and it is said that it is related to the cases of genetic disorders or mutations that usually occur in normal cells. Malignant tumor transformation depends on changes in 2 types of genes. Oncogenes can be activated as a result of many changes, which can be caused by genetic mutation and a number of epigenetic changes. However, despite this, cis suppressor genes can fully regulate cell proliferation under normal conditions and maintain the overall stability of the genome [1]. Although Knudson's '2-hit' model has taken a number of important steps to explain information about the loss of activity of sis genes, subsequent studies have shown that inactivation of sis genes can occur by more complex means, such as insufficiency and negative dominant effect [2]. Recently, the development of the next-generation sequencing method and the genetic characteristics of different species of shark have been possible. Essentially, The Cancer Genome Atlas has revealed somatic mutations, genetic structural differences, and changes in gene expression in various ways in many malignant tumors [3]. This type of research has helped to find many changes, including insertions, deletions, and chromosomal anomalies. These differences mainly manifested themselves in several genes - oncogenes such as EGFR, KRAS, and BRCA1, BRCA2 in tumor cells [1], [4]. The genetic basis of the risk of cancer is derived from many elements, cloned sis consists of differences and germlines that increase susceptibility to sis. It has been investigated that hereditary genetic cancer risk and cancer treatment can have a

high impact on mammary gland and ovarian cancer and Lynch syndrome [4], [5]. Recent studies show that germline genetic differences have a 20% chance of ovarian cancer and 5% of endometrial cancer [6]. In addition, molecular biomarkers have an important role in the diagnosis and treatment of cancer. Biomarkers can be used as more useful tools than previously thought; such biomarkers include microsatellite instability, cis mutational burden, and gene expression markers. Through this, stratification of patients and making therapeutic decisions can be easier [7], [8].

Liquid biopsy has emerged as a minimally invasive method for the genetic assessment of tumor cells in the blood, as well as for monitoring treatment responses and the changes that occur during therapy [7]. Tumor development primarily arises from the progressive accumulation and interaction of numerous genetic alterations during cancer evolution. Differences in genetic characteristics among various cancer cell subpopulations within the same tumor can lead to the formation of tumor heterogeneity. Such genetic diversity can influence a range of clinically significant characteristics, including tumor aggressiveness, metastatic potential, risk of recurrence, and response to medical treatments [9]. Furthermore, treatment-resistant subclones may be present within the tumor even before therapy is initiated. During treatment, these resistant cell populations can rapidly multiply, ultimately leading to treatment failure and, in some cases, disease progression and death. Genomic profiling has become increasingly important in determining the molecular characteristics that underlie tumor behavior and influence clinical treatment outcomes. Among the genomic alterations identified to date, driver mutations are considered the primary molecular anomalies. The reason for this is considered to be their role in the disruption of key signal transduction pathways associated with aberrant proliferation and tumor development. Constitutive activation of the RAS-RAF-MEK-ERK and PI3K-AKT-mTOR signaling pathways can accelerate metastasis by completely halting apoptotic activity in malignant tumors [10].

As a result, genetic alterations affecting KRAS and BRAF have attracted particular attention. The primary reason for this is that these alterations can significantly influence the efficacy of molecularly targeted therapies. Moreover, genetic alterations affecting DNA damage response and repair pathways, particularly in genes such as BRCA1, BRCA2, ATM, and PALB2, may contribute to cancer susceptibility and influence the response of tumor cells to specific therapeutic approaches [11]. The disruption of DNA repair mechanisms in cancer cells can lead to the emergence of molecular vulnerabilities. This disruption may create opportunities for the development of more selective and effective treatment methods.

2. Genetic Variants in Cancer & Somatic Mutations

Mutations occurring in somatic cells lead to genetic changes that play a decisive role in the onset and development of cancer in humans. This process can occur in various cells in humans throughout their lives [12]. First of all, they arise from various intracellular processes, such as anomalies occurring during DNA replication or problems caused by oxidative stress. However, such changes can also occur due to the influence of factors such as smoking and intense ultraviolet (UV) radiation [13].

Driver and passenger mutations differ significantly from each other in terms of their mutational mechanisms. Thus, driver mutations contribute to the survival of cancer cells by delaying programmed cell death and activating cellular processes associated with proliferation, growth, metastasis, and tumor formation. Unlike driver mutations, passenger mutations are considered to be of minor biological significance. Since they do not directly participate in tumor development, they are understood to have a limited functional impact on cancer progression [14]. The frequency and nature of somatic mutations can vary significantly depending on the tissue type. These changes reflect differences in environmental impacts and tissue-related biological processes [14]. These changes reflect differences in environmental impacts and in the biological processes occurring within the tissue [14]. In this context, the importance of comprehensive genomic profiling in the assessment and clinical management of cancer is emphasized [15].

Genetic abnormalities can disrupt a range of cellular processes by altering the structure or expression of proteins involved in the regulation of cell proliferation, division, and survival, ultimately affecting normal cellular functions.

A range of genetic alterations, including missense, nonsense, and frameshift mutations, along with chromosomal abnormalities, may alter gene expression or impair protein function. Thereby contributing substantially to the malignant transformation of normal cells. As a result of these genetic changes, a direct link is established between genomic instability and both the initiation and progression of cancer. Changes occurring in somatic cells can disrupt the activity of numerous genes that play a crucial role in fundamental biological processes such as apoptosis, DNA damage repair, cell cycle regulation, cell differentiation, and the maintenance of genomic stability. Mutations affecting the activity of genes involved in these mechanisms can disrupt normal regulatory pathways, thereby promoting uncontrolled and abnormal cell proliferation. Alterations in the oncogene activation mechanism can trigger sustained signal transduction pathways that promote intensive cell proliferation. Otherwise, the complete inactivation of tumor suppressor genes could disrupt the functioning of essential cellular mechanisms that ensure cell division and the maintenance of genomic integrity [16]. The functional mechanism of a genetic alteration is determined by the characteristics of the affected gene, the precise location of the mutation within the genome, and its effects on protein synthesis and transcriptional regulation.

The fundamental essence of the clonal evolution of tumors is characterized by the accumulation of somatic mutations. As cancer cells progress through the stages of proliferation, new genetic changes occur within them. This results in the emergence of genetically distinct subpopulations within the same tumor. Sometimes, tumor subclones can possess specific biological advantages. These advantages include increased metastatic potential of cells and their proliferative capacity, as well as high resilience to environmental stress factors and to anti-cancer treatments [17].

3. Molecular Biomarkers

Germline variants arise from changes occurring in the cell of one of the parents. Specifically, the resulting alteration establishes heritable genetic differences that persist in all cells of the next generation, originating from the early stages of reproductive cell development [2]. These changes are observed in various forms, ranging from single nucleotide polymorphisms (SNPs) to larger-scale structural genomic alterations. In addition to susceptibility to cancer, this factor may also influence the course of the disease and the response to treatment [4].

Studies show that hereditary breast and ovarian cancer, Li-Fraumeni syndrome, and Lynch syndrome arise from mutations in genes such as BRCA1, BRCA2, and TP53, as well as in the mismatch repair genes MLH1 and MSH2 [5]. The impact of genetic variations on the risk of developing cancer depends primarily on the biological function of the genes in which the alterations occur. Furthermore, a link has been established between cancer development and the level of risk associated with the specific type of cancer.

Mutations in genes responsible for maintaining genome stability can be considered one of the key factors significantly increasing the likelihood of malignant tumor development in the organism. The BRCA1 and BRCA2 genes, which are responsible for the repair of DNA double-strand breaks, are considered key components of the homologous recombination pathway. Defects occurring during the repair process create an additional risk of genomic anomaly accumulation. This can lead to an increased likelihood of developing various malignant tumors, such as breast and ovarian cancers [18].

The presence of hereditary defects in DNA repair pathways reflects a molecular link between genetic predisposition and the development of cancer. However, the impact of inherited genetic alterations on the functioning of DNA mismatch repair systems is considered a key factor. Consequently, this process can lead to increased susceptibility to cancer. Lynch syndrome is considered one of the factors that significantly increase various health risks. Pathogenic germline variants in mismatch repair genes disrupting the DNA repair mechanism and increasing genomic instability is an example of this. This also leads to an increased risk of developing endometrial, colorectal, ovarian, and other malignant tumors [19]. Cancer cells arising from defects in DNA repair often exhibit microsatellite instability. This is considered a molecular characteristic of significant biological and clinical importance.

4. Conclusion

Significant strides have been made in cancer research through advances regarding molecular genetic variants and

biomarkers. These achievements have substantially broadened scientific understanding and perspectives concerning the molecular biology, pathogenesis, and clinical characteristics of cancer.

A comprehensive analysis of germline variants and somatic genomic alterations enables a more precise molecular characterization of tumors, the refinement of prognostic assessment mechanisms, and the development of personalized treatment strategies. Comprehensive analysis of germline variants and somatic genomic alterations enables a more precise molecular characterization of tumors. Such characterization lays the groundwork for improving the prognostic assessment of these alterations and developing personalized treatment strategies.

The application of key molecular biomarkers, such as tumor mutational burden (TMB), microsatellite instability (MSI), and gene expression profiles, in clinical practice is of great importance in medicine. In recent years, significant progress has been made using these markers to select optimal treatment approaches, refine diagnostic assessments, and more effectively evaluate treatment responses. This increasingly enhances the importance of these molecular markers in modern oncology. In particular, the use of molecular biomarkers plays a crucial role in identifying patients who may potentially benefit from immunotherapy and in making decisions regarding the selection of adjuvant systemic treatment approaches.

Advancements in the fields of cancer genetics, bioinformatics, and artificial intelligence will play a crucial role in the future integration of genomic and clinical data. In particular, the use of bioinformatics and artificial intelligence is expected to contribute to improvements in early disease diagnosis and treatment decision-making. This, in turn, will lead to significant progress in oncology. At the same time, attention must be paid to key aspects regarding the integration of molecular research findings into daily clinical practice. Specifically, integrating research results into routine clinical practice requires comprehensive clinical validation, as well as thorough consideration of multidisciplinary collaboration, ethical issues, and technical and practical limitations. Such achievements in scientific fields are accelerating the transition from traditional treatment to personalized therapy tailored to the patient's clinical indicators and the molecular-biological characteristics of the tumor.

Author Contributions

The sole author is responsible for conceptualizing, collecting, and analyzing data, and writing and editing the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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