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Differential Analysis and Application Prospects of DNA Tumor Biomarkers in The Five Major Types of Tumors

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Abstract. With the increasing global burden of cancer, the study of tumor biomarkers (TMs) is of great significance as key tools for early diagnosis, disease monitoring, treatment efficacy evaluation, and prognosis judgment of cancer. This study focuses on the five major tumor types: lung cancer, colorectal cancer, liver cancer, female breast cancer, and gastric cancer. By screening and integrating relevant data on the clinVar website, this article classified, quantified, and analyzed the differences in DNA TMs identified in the five major tumor types mentioned above. In addition, this article explores the mechanisms and principles of DNA tumor biomarker types with relative commonality and specificity in tumor formation and spread among the five major tumor types. We found that the mechanism characteristics of common TMs in the five major tumor types are relatively concentrated; The mechanism characteristics of TMs unique to the five major tumor types are more dispersed. The frequency of occurrence of DNA tumor biomarker mechanism classification has a certain directional effect on tumor types and has a positive impact on the judgment of tumor types. This study aims to provide theoretical support for the discovery, refinement, and personalized clinical application of more TMs in the future, and to improve the survival rate and quality of life of cancer patients.

Keywords: Tumor biomarkers; DNA; differential analysis; detection techniques; clinical applications.

1. Introduction

Biomarkers are biomolecules found in tissues, blood, and other bodily fluids, which are normal or abnormal processes and signs of a certain condition or disease [1]. They can observe the body's response to a certain disease or treatment. TMs refer to substances produced by tumors or the body's response to tumors during the occurrence and progression of tumors, which exist in tumor tissues or body fluids such as blood, saliva, feces, and urine [1]. TMs have a long history of development and have become relatively mature. In the past few decades, researchers have continuously made progress in the exploration and discovery of novel, sensitive, specific, and accurate TMs [1]. Due to the proven critical value of TMs in cancer screening and early diagnosis, prognosis prediction, recurrence detection, and treatment efficacy monitoring, they remain one of the hot topics in biomedical research.

The International Agency for Research on Cancer of the World Health Organization pointed out in the 2022 edition of the global cancer statistics report that lung cancer is the main cause of cancer death, with a mortality rate of 18.7% [2]. The second is colorectal cancer (mortality rate is 9.3%), followed by liver cancer (mortality rate is 7.8%), female breast cancer (mortality rate is 6.9%), and gastric cancer (mortality rate is 6.8% [2]. Therefore, five major tumor types, namely, lung cancer, colorectal cancer, liver cancer, female breast cancer, and gastric cancer, are major threats to human health at present.

Among these five main types of tumors, a large number of TMs have been discovered or manufactured, with DNA being particularly prominent. However, we have found that most of the TMs discovered in scientific research currently lack authority and cannot be applied clinically. At the same time, there is relatively little research on the differential analysis and mechanism organization of TMs among the main types of tumors. Therefore, we will summarize the similarities and differences in the types, functions, and related signaling pathways of authoritative TMs in different tumor types, and explore the biomedical mechanisms and principals involved. This will have a positive impact on the discovery and rational application of more and more reliable TMs in the future.

This article will explore the similarities and differences of DNA TMs among the five major types of tumors, their underlying mechanisms and principles, as well as clinical application prospects by organizing and analyzing relevant data. TMs, as an important research direction, have relatively mature research progress but still have certain development potential. Comparative analysis of differences in DNA TMs for current major cancers is innovative, providing guidance for the discovery and clinical application of future biomarkers. In addition, personalized combinations of TMs can improve the level of precision medicine, broaden future research perspectives, and accelerate research progress in clinical classification and targeted treatment of cancer patients.

2. Methods

To collect authoritative information on known TMs, the tumor biomarker data in this article was obtained from ClinVar. ClinVar is a freely accessible public database used to archive and summarize information on the relationship between human gene variations and their related clinical significance（https://www.ncbi.nlm.nih.gov/clinvar/）[3]. ClinVar is managed by the National Center for Biotechnology Information (NCBI) in the United States and collects data from various sources, including research, clinical testing laboratories, expert groups, and individual researchers. To ensure the authority of the selected data, this article selected data from an expert group for differential analysis of TMs. This article first analyzes the duplication of DNA TMs in five main tumor types and selects DNA TMs that appear in all five main tumor types as well as DNA TMs that only appear in a specific type among these five tumor types. Secondly, we conducted a qualitative analysis of the common and specific genes among these five types of tumors, as well as the mechanisms and principles of DNA TMs that are relatively common and specific in the process of tumor formation and spread. Finally, due to the lack of regularity in the qualitative analysis results, this study conducted a queue study on multiple tumor types and quantitatively analyzed the grouping types of DNA TMs among the five major tumor types.

3. Results

3.1. Data Features

Through the collection and screening of data from the clinVar database, we have compiled data on DNA TMs among the five major tumor types that have been confirmed by the expert team. A total of 113 authoritative DNA TMs or tumor biomarker combinations related to the five major tumor types were screened. To facilitate a more intuitive display of data features, we analyzed the duplication of tumor markers among the five major tumor types.

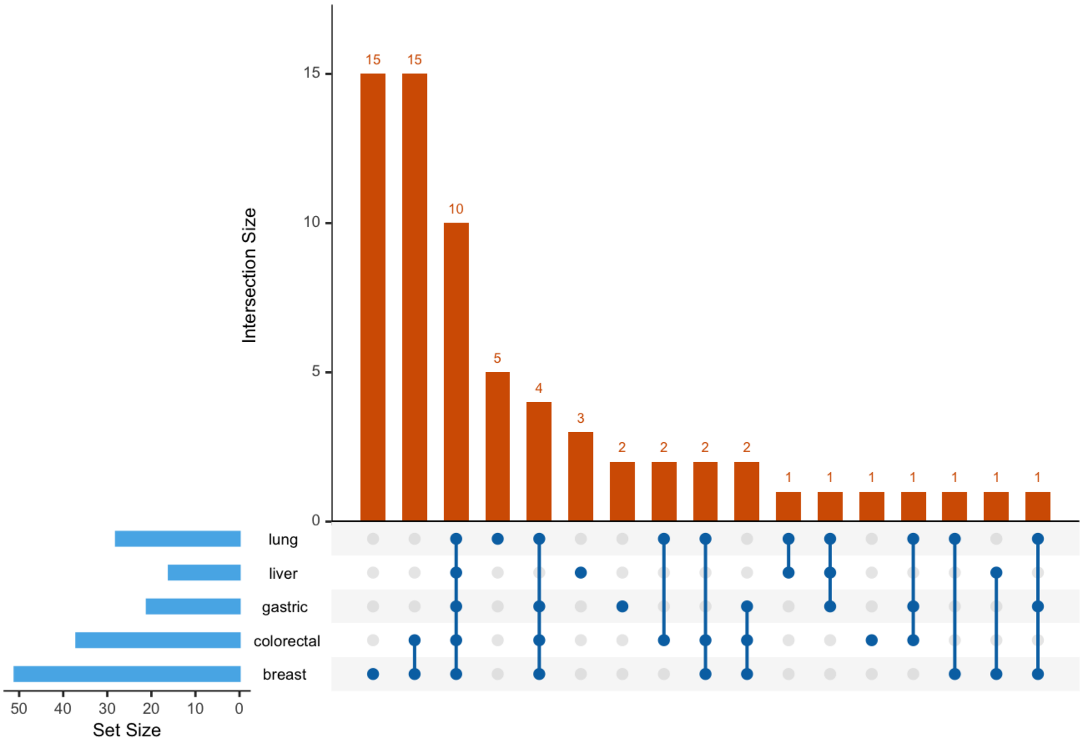

Fig. 1 Upset plot of DNA tumor biomarkers among the five major tumor types

Figure 1 shows an upset plot of DNA TMs in the five major tumor types, reflecting the cross-over of DNA TMs among the five tumor types. The blue horizontal bar chart in the bottom left corner of Figure 1 represents the number of DNA TMs in each tumor type. The dot plot below Figure 1 represents the repeat types of DNA TMs in the five major tumor types, and the vertical bar chart corresponding to each repeat type represents the number of TMs under that repeat type. The main body of Figure 1 represents the duplication of DNA TMs among the five major tumor types. The third column in the main body of Figure 1 represents the distribution of a specific DNA tumor biomarker across the five major tumor types.

3.2. Mechanism of DNA Tumor Biomarkers: Qualitative Analysis

Figure 1 intuitively reflects that there are 10 DNA TMs distributed in all five types of tumors, and there are also DNA TMs with relative specificity in the five types of tumors. By querying the main mechanisms and principles of how these 10 DNA TMs affect tumor formation, we have classified the mechanisms by which DNA TMs affect tumor formation. The classification results are as follows:

1) Genetic alteration: The upregulation or downregulation of the expression levels of oncogenes and tumor suppressor genes due to genetic changes directly affects tumor formation.

2) Epigenic modifications: Indirectly affecting the formation and spread of tumors due to DNA methylation or histone modifications affecting gene expression.

3) DNA Repair and Genomic Stability: Proteins expressed by genes participate in the repair of gene replication errors; Mismatch repair (MMR) or gene involvement in cellular repair of DNA double-strand breaks; Homologous recombination repair (HRR) indirectly causes the loss of control of tumor cells due to the loss of gene function.

4) Signaling Pathways: Proteins expressed by genes are related to signaling pathways that affect cell growth, survival, and migration. Changes or loss of gene function can indirectly lead to the formation of tumor cells.

5) Metabolic Reprogramming: Changes in gene function cause alterations in metabolic pathways that support rapid cell growth, such as glycolysis and mitochondrial metabolism, leading to uncontrolled growth of tumor cells.

6) Immune Response and Inflammation: Proteins expressed by genes are molecules that regulate immune evasion and inflammation, such as immune checkpoint-related genes, which play a key role in the formation of tumor cells.

7) Microenvironment and Angiogenesis: Proteins expressed by genes are factors that mediate the interaction between tumor cells and the surrounding matrix, playing an important role in the tumor microenvironment and angiogenesis around the tumor.

By further categorizing and organizing the mechanisms of common and specific DNA TMs, we have identified five common DNA TMs among tumors. In addition, we visualized this information.

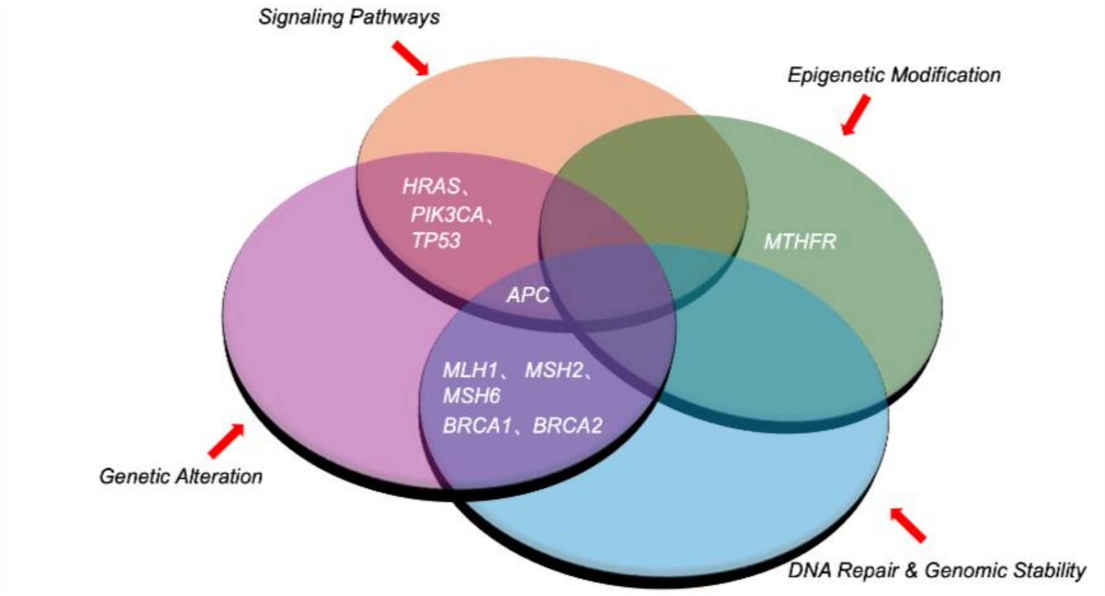

Fig. 2 Venn diagram of the distribution of common DNA tumor biomarkers among the five major tumor types

As shown in Figure 2, the distribution of DNA TMs shared by most of the five major cancers is relatively concentrated. Among them, the APC gene (adenomatous polyposis coli) simultaneously conforms to four types of DNA TMs: genetic alteration, signaling pathways, and DNA repair & genomic stability. The APC gene, as an important tumor suppressor gene, is also involved in intracellular DNA repair and regulation of the Wnt/β - cateninignaling signaling pathway, making it the most common mutated gene in cancer [4,5]. In addition, common DNA TMs such as BRCA1 (breast cancer gene 1), BRCA2 [6], and MLH1 (mutL homolog 1) [7] simultaneously conform to both genetic alteration and DNA repair & genomic stability types of DNA TMs. HRAS (The Harvey rat sarcoma) [8], PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) [9], and TP53 (tumor protein p53) [10,11] all conform to both genetic alteration and signaling pathways as DNA TMs. The unique feature is the MTHFR (methylenetetrahydrofolate reductase) gene. MTHFR generates methylenetetrahydrofolate reductase, which converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is crucial for DNA methylation. MTHFR dysfunction can lead to elevated homocysteine levels, decreased availability of folate, and abnormal DNA methylation, all of which can contribute to the development of cancer [12]. In summary, most of the DNA TMs commonly present in tumor types are associated with abnormal expression of oncogenes and tumor suppressor genes, DNA repair mechanisms, and key signaling pathways. These are the most common mechanisms and principals involved in the generation and spread of tumor cells.

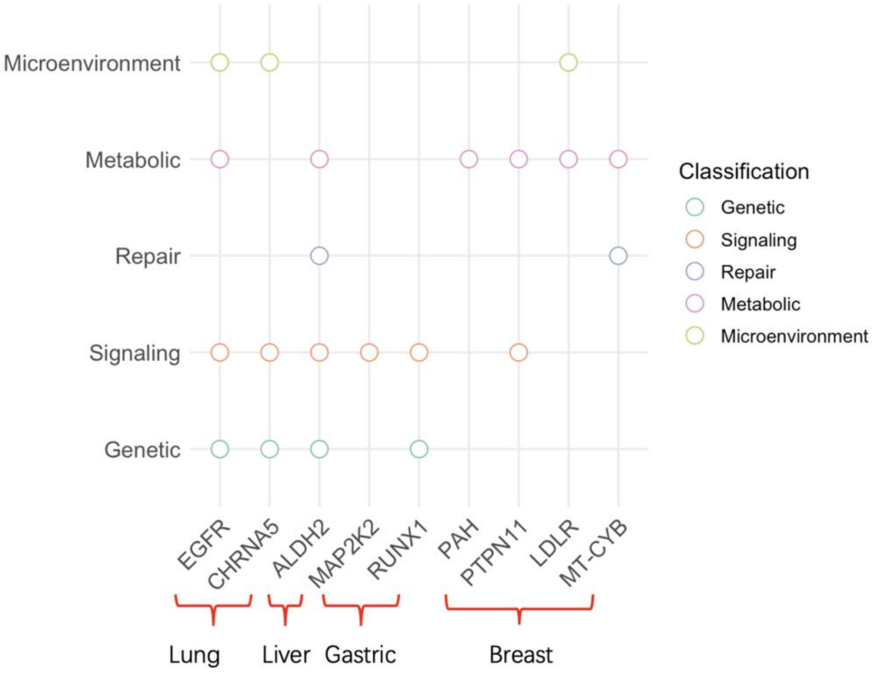

Fig. 3 Dot plot of the distribution of specific DNA tumor biomarkers in the five major tumor types

Figure 3 reflects the distribution of relatively specific TMs in terms of their mechanisms and principles among the five major tumor types. Figure 3 shows the types of DNA TMs sourced by the expert group on the clinVar website that only appear in any one of the five major tumor types, and exclude sites with unclear functions. Figure 3 is presented in the form of a dot plot, where the x-axis represents unique genes and their associated tumor types, and the y-axis represents classification types. The dot plot represents the combination of various tumor biomarker mechanisms and classification features. Among them, DNA TMs specific to lung cancer, such as CHRNA5 (Cholinergic Receptor Nicotinic Alpha 5 subunit) and EGFR (epidermal growth factor receptor), are associated with three types of mechanisms. They are Microenvironment and Angiogenesis, Signaling Pathways, and Genetic Alteration, which may be related to the high metastasis of lung cancer. The specific types of DNA TMs in breast cancer are all related to the mechanism type of metabolic reprogramming. This may indicate that metabolic processes play an important role in the process of breast lesions.

3.3. Mechanism of DNA Tumor Biomarkers: Quantitative Analysis

The results of qualitative analysis lack regularity, and a single database affects the credibility of research findings. So, this article also used a cohort study conducted in 2017 for quantitative analysis of multiple tumor types [13] and visualized the proportion of each DNA tumor biomarker mechanism classification type in the five major tumor types.

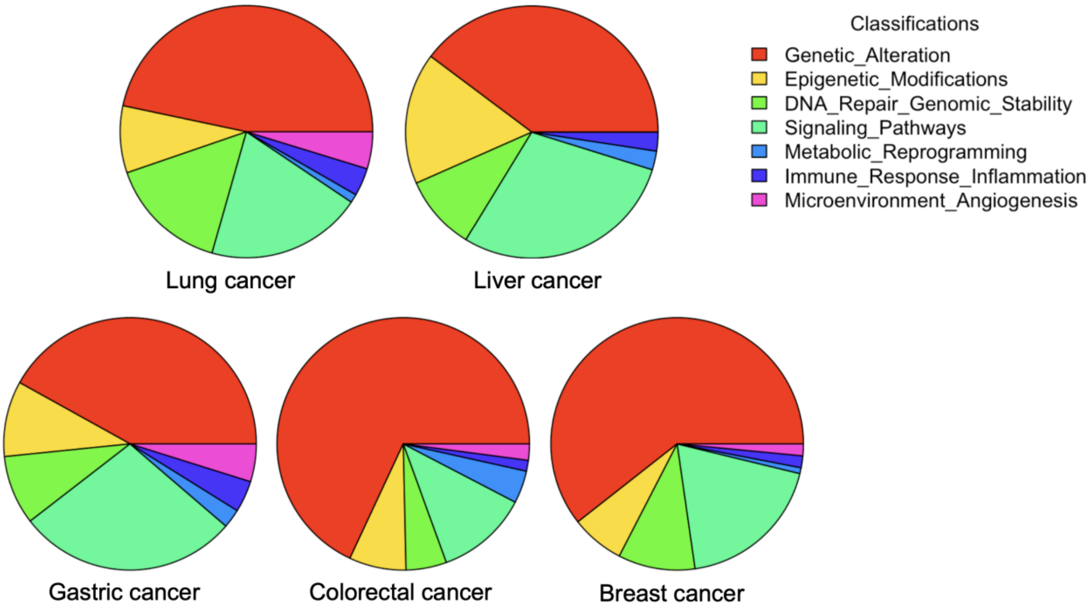

Fig. 4 Pie chart of the proportion of tumor biomarker mechanism classification among the five major tumor types

Figure 4 shows the proportion of each tumor biomarker mechanism classification type among the five major tumor types. Among them, genetic alteration, DNA repair and genomic stability, and signaling pathways account for a large proportion of any tumor type, which is consistent with the qualitative analysis of the common gene mechanism classification mentioned earlier. These three mechanisms are important factors in the formation and spread of tumor cells. At the same time, the conclusions of qualitative analysis on the classification of specific gene mechanisms are somewhat different from the results of quantitative analysis. For example, the proportion of Metabolic Reprogramming in breast cancer is relatively low, which indicates that the representativeness of previous TMs is problematic. After quantitative analysis, we found that there was no significant difference in the proportion of DNA tumor biomarker mechanism classification among different tumor types. This indicates that there is no significant difference in the mechanism level among different tumor types, only differences exist in relatively specific mechanism types.

4. Discussion

Most of the currently discovered and certified DNA TMs are related to key biological mechanisms such as intracellular control of cell growth, metastasis, and survival. And the number of TMs with specificity still accounts for a minority. Meanwhile, the mechanisms related to tumors themselves are complex, and due to the highly dynamic nature of tumors, different types of tumors also have the possibility of metastasis. Therefore, relying solely on a combination of DNA TMs cannot accurately locate specific tumor types. In the future, more TMs related to specific mechanisms and principles in specific tumor types need to be discovered and determined. In addition, due to the relatively single database used in this study, the results may have a certain degree of randomness; The research results are a reasonable guess and summary of the data characteristics of current DNA TMs at the mechanism and principal level, so there is a lack of certain experimental verification. Future researchers can use more extensive data analysis and organization, and conduct experimental verification.

In clinical samples, tumor DNA has shown promising prospects for early detection, prognosis, monitoring, and treatment selection as a single analyte or in combination with other analytes [14]. However, there are currently few TMs that have been truly put into clinical use. TMs are prone to interference in detection, and the accuracy of detection is difficult to guarantee. At the same time, there are issues with the inability to achieve multi-center, large-scale, and long-term clinical trials in clinical applications. In addition, due to the low sensitivity of asymptomatic tumor DNA as a tumor biomarker and the influence of concurrent comorbidities, the specificity may be low among screened subjects [14,15]. To determine the true performance and clinical practicality of these tests, it is necessary to conduct prospective studies with a large number of cases and more controls. Future research can focus more on the joint analysis of multiple TMs and develop a technology platform that can monitor changes in biomarkers. In addition, future researchers can strive to establish systematic clinical trials on TMs to improve credibility and accuracy. The discovery of new biomarkers with appropriate specificity, sensitivity, and reliability will provide evidence for personalized decision-making in the overall management of cancer patients [15]. Through these efforts, we are expected to achieve personalized treatment based on multidimensional data containing DNA TMs, improving the precision and effectiveness of anti-tumor therapy.

5. Conclusion

Through systematic research on DNA TMs, we found that the mechanism characteristics of common DNA TMs in the five major tumor types are relatively concentrated. Mainly related to mutations in oncogenes or tumor suppressor genes, DNA repair mechanisms, and signaling pathways; The mechanism characteristics of DNA TMs unique to the five major tumor types are more dispersed, and each tumor biomarker has a relatively specific mechanism classification combination. The high frequency of specific mechanism classification in unique DNA TMs of a certain tumor type is also correlated with the characteristics of that tumor type. For example, the high frequency of tumor microenvironment and angiogenesis in lung cancer as well as the high frequency of metabolic reprogramming in liver cancer. However, this study has a certain degree of randomness and lacks experimental verification. This article analyzes and summarizes the commonalities and specificities of currently discovered DNA TMs in major tumor types, and focuses on the insufficient accuracy and specificity of current TMs in clinical applications. We hope that these studies can provide theoretical support for the discovery, refinement, and personalized clinical applications of more TMs in the future, and achieve personalized treatment based on multidimensional data containing DNA TMs.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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