Application and Mechanism of Multi-omics Technology in the Treatment of Colorectal Cancer

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Abstract. Colorectal cancer is a common type of malignant tumor. The accurate diagnosis and treatment need to be based on molecular mechanism analysis. Multi-omics technology integrates multi-level molecular information, which makes it a “sally port” for overcoming traditional cure. This integration helps break through the limitations of single-level research. This paper will focus on the application and mechanism of multi-omics technologies in the treatment of CRC. The outcome shows that genomics can locate therapeutic targets by identifying mutations in driver genes (APC and KRAS). Transcriptomics forecasts tumor classification and drug sensitivity by analyzing RNA expression patterns. Proteomics verifies the difference in functional proteins like PL3K and PD-L1. Metabolomics discovers the characteristic metabolite, such as oleic acid. Microbiomics find that gut microbiota promotes cancer through the synergistic interaction with metabolites and inflammation. These omics perspectives are not isolated but interrelated in revealing tumor characteristics. This paper will integrate the mechanisms and strategies from multiple omics perspectives and provide multiple dimensions for an accurate cure of CRC.

Keywords: Colorectal cancer; multi-omics; precise treatment.

1. Introduction

Colorectal cancer is a highly prevalent malignant tumor around the world; the traditional cure has an imitative curative effect, especially for patients in the middle and late stages due to the tumor heterogeneity. Multi-omics technology combines genomic, transcriptomic and other multi-level molecular information to provide an important instrument for analyzing the pathogenesis and optimizing the cure strategy [1]. The multi-omics study conducted by the Chinese Academy of Sciences (CAS) on 1063 colorectal cancer samples identified 96 driver gene mutations and established a prognostic classification system. This significantly increases the accuracy of the cure [1]. Kunming Medical University selected 17 combinations of metabolites by analyzing metabolomics, which include plasma and feces. This makes the sensitivity and specificity of early diagnosis exceed 90% [2]. Those studies verify that multi-omics have become the core of precision medicine for colorectal cancer.

The multi-omics research now has covered the multi-molecular levels of tumor occurrence. Genomics clearly illustrates the crucial role of gene mutations such as APC and KRAS. About 80% of patients have an APC mutation caused by uncontrolled cell proliferation [1,3]. Transcriptomics achieves tumor classification through RNA expression patterns and the KRAS mutant subtype shows a poor response to cetuximab, which provides a reference for pharmacy [4]. Proteomics verified the abnormal activities of proteins such as PI3K and PD-L1. The PIK3CA mutation can activate the PI3K pathway to promote cancer [5]. Metabolomics reveals the dependence of tumors on glutamine, which means CB-839 and other antagonists can stop the energy provided [6]. Microbiomics has revealed that bacterial communities such as Fusobacterium can damage the intestinal barrier and trigger inflammation to promote cancer [7,8].

At the same time, the integration of multi-omics data has driven the innovation of treatment strategies. For instance, the causal chain of PIK3CA gene mutation (genomic level) → activation of PI3K (proteomic level) → upregulation of glutamine transporter (transcriptomic level) → active metabolism (metabolomic level) provides theoretical support for PI3K inhibitor + glutamine

antagonist combination regimen. This scheme has a significant inhibitory effect on PIK3CA mutation tumors compared to a single drug [6].

2. Omics related to Colorectal Cancer

2.1. Genomics

Genomics focuses on mutations in DNA within cells. In high school, we learned that tumor suppressor genes can prevent abnormal cell proliferation, while oncogenes regulate normal cell growth. Mutations in these two types of genes are common causes of cancer. For colorectal cancer, APC gene is one of the common tumor suppressor genes, and about 80% of patients will have this gene mutatio[1]. In addition, the KRAS gene and BRAF gene are both oncogenes that continuously transmit growth signals to cells, leading to tumor invasion and metastasis [3]. These gene mutations do not exist in isolation. The study of 1063 colorectal cancer samples by the Chinese Academy of Sciences found that 96 gene mutations would jointly promote the occurrence of tumors. For patients with PIK3CA gene mutation, the demand of tumor cells for glutamine (Gln) will increase, which provides a target for subsequent treatment [1].

2.2. Transcriptomics

The activity of genes is reflected through the transcription process, and transcriptomics reveals abnormalities in gene regulation by analyzing RNA expression patterns. In colorectal cancer, genes closely related to cell division, such as CCND1, transcribe more RNA, thereby accelerating cell division [9]. In addition, transcriptomics helps to classify different types of tumors. Scientists have classified colorectal cancer into five subtypes by analyzing RNA expression patterns. Subtypes carrying KRAS mutations have poor response to cetuximab, due to the low activity of the EGFR signaling pathway in these tumors, resulting in unsatisfactory efficacy of cetuximab [4].

2.3. Proteomics

Proteins are the "executors" of genetic instructions, and proteomics aims to detect the expression and functional changes of these "executors". For example, carcinoembryonic antigen (CEA) is normally present in relatively low levels in human blood, but in colorectal cancer patients, CEA levels can increase, allowing doctors to detect whether the condition has recurred after surgery [5]. PI3K protein is another type of 'executor'. When the PIK3CA gene mutates, the PI3K protein is abnormally activated and continues to transmit proliferation signals to cells. In addition, when the expression of SIRT2 protein decreases, immune cells (CD8+) in the tumor microenvironment will aggregate, indicating that inhibiting SIRT2 can improve therapeutic efficacy [5].

2.4. Metabolomics

Tumor cells grow faster and have significantly different metabolic patterns from normal cells. Metabolomics reveals these abnormalities by monitoring changes in metabolites. A study conducted by Kunming Medical University shows that the level of oleic acid in the blood of colorectal cancer patients is significantly increased. Oleic acid can bind to ENO1 protein and activate the PI3K/Akt pathway, thereby accelerating tumor growth. In addition, the reduction of bile ketone can weaken the activity of the MAPK pathway [10]. In addition, researchers have found that 17 plasma metabolite combinations can be used to detect early colorectal cancer, with accuracy, sensitivity, and specificity all exceeding 90% [2]. Colorectal cancer cells also require glutamine (Gln), which can provide a raw material for DNA synthesis. Therefore, drugs that inhibit glutamine metabolism (such as CB-839) can help prevent tumor growth [6].

2.5. Microbiology and Intestinal Environment

The gut microbiota, as an important component of the host microenvironment, can also have an impact on tumors. A study by Peking University has shown that the number of pathogenic bacteria such as Fusobacterium nucleatum in colorectal cancer patients increases. The butyrate they secrete can break down the intestinal barrier and cause chronic inflammation, and in some cases, promote tumor development. Conventional Bacteroides can help tumor cells synthesize nucleotides, leading to chemoradiotherapy resistance [7]. Porphyromonas gingivalis in the oral cavity can enter the intestine through the bloodstream and activate NLRP3 inflammasome, thereby promoting tumorigenesis [8]. This means that the intestinal environment is like the "soil" for tumor growth, and microbial imbalance can make tumors more prone to growth.

3. Integration Logic of Multimodal Omics Data

The above-mentioned single omics studies reveal molecular abnormalities in colorectal cancer from the perspectives of DNA mutations, RNA expression, protein function, metabolite changes, and microbial interactions. However, the occurrence and development of tumors are the result of the synergistic effects of multiple molecular layers. Therefore, it is necessary to integrate and analyze multimodal omics data to construct a complete molecular regulatory network. Multimodal omics has important value in causal relationship research, as it is like a molecular chain: gene mutations are the source, which can cause changes in transcriptome expression, thereby altering proteomic function, ultimately reflected in metabolic abnormalities, while the microbiome interacts with the host molecular network through metabolites or signaling pathways.

From a technical perspective, the integration of multimodal omics data is mainly achieved through the following steps. Firstly, data standardization and normalization are used to address the heterogeneity of different omics data, such as mutation frequency in the genome, FPKM values in the transcriptome, peptide intensity in the proteome, and peak area in the metabolome. Z-score standardization, logarithmic transformation, and other methods are employed to eliminate dimensional differences and ensure comparability of the data. The second is feature selection and dimensionality reduction, using differential analysis (such as DESeq2 for transcriptomics and limma for proteomics) to screen key disease-related features in each omics, and then using methods such as principal component analysis (PCA) and t-distributed neighborhood embedding (t-SNE) to reduce data dimensionality and minimize noise interference. The third is the construction of association analysis models, which use canonical correlation analysis (CCA) to explore the covariate relationship between the genome and transcriptome. Partial least squares path model (PLS-PM) is used to analyze the causal relationship between the proteome and metabolome, or Bayesian network is used to infer the regulatory direction between multiple omics features (such as the cascade effect of gene mutation → gene expression → protein activity). The fourth is network integration and functional annotation. A "gene protein metabolite" interaction network is constructed through weighted gene co expression network analysis (WGCNA) or STRING database, combined with gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) annotation, to clarify the biological functions of network modules (such as cross omics activation of PI3K/Akt pathway). For example, when the PIK3CA gene undergoes a mutation, association analysis between the genome and transcriptome reveals upregulation of the downstream target gene SLC1A5 (glutamine transporter) expression. Combined with proteomic data, the phosphorylation activation of PI3K and AKT proteins can be verified, while metabolomic data further shows an increase in intracellular glutamine content. Finally, the key pathway of "PIK3CA mutation → SLC1A5 up regulation → increased glutamine uptake" was confirmed through network modeling [6]. This molecular chain indicates that blocking PI3K alone is not enough. If glutamine antagonist (CB-839) is used simultaneously, it can better inhibit tumors. Preclinical studies have shown that this combination therapy has significant therapeutic effects on tumors caused by PIK3CA gene mutations [5]. The gut microbiota is an external influencing factor, for example, the production of trimethylamine oxide (TMAO) by the microbiota

can enter the bloodstream and promote inflammatory reactions, which in turn can make the metabolism of tumor cells more active. This means that targeted microbial metabolites can also be used as adjuvant therapy [7].

4. Multimodal Analysis of the Pathogenesis of Colorectal Cancer

4.1. Genomic Mutations

The first abnormality to occur is the APC gene mutation. The normal APC gene can expel β - catenin from the cell. After mutation, β - catenin will accumulate in the cell and enter the nucleus, activating the WNT pathway, leading to rapid cell division and the formation of precancerous polyps[1]. As the condition progresses, the TP53 gene also undergoes mutations, and the mutated cells' DNA damage cannot be repaired, thereby acquiring the ability to invade and spread to surrounding tissues [3].

4.2. Transcriptome Abnormalities

After gene mutation, abnormal gene expression may occur. For example, KRAS mutations activate the MAPK pathway, which promotes extensive transcription of MYC and CCND1 genes. MYC can promote protein synthesis in cells, while CCND1 can rapidly induce cell division. The synergistic effect of the two can double the rate of cell proliferation [9]. Transcriptome studies also found that the expression of genes related to epithelial mesenchymal transformation was high in stromal subtype tumors, and such cells were more likely to fall off from the primary site and metastasize [1].

4.3. Proteome

The RNA generated by transcription will eventually synthesize proteins and exert its function. The V600E mutation in the BRAF gene is a typical example, which causes sustained activity of the BRAF protein, leading to phosphorylation of MEK and ERK proteins, which are transmitters of cell growth signals [4]. In the tumor microenvironment, high expression of PD-L1 protein is also crucial as it affects T cell function and prevents the immune system from recognizing tumors [5].

4.4. Metabolome

Tumor cells have obvious metabolic habits. Glutamine not only provides the nitrogen required for protein synthesis, but also generates energy through the malate aspartic acid shuttle. The accumulation of fatty acids such as oleic acid can activate the PI3K/Akt pathway and enhance cell viability [10]. These metabolic processes provide energy for tumors, enabling them to continue growing.

4.5. Synergistic Effect of Intestinal Environment

The gut microbiota promotes cancer occurrence in various ways. FadA, the adhesion protein of Fusobacterium nucleatum, can bind to E-cadherin in intestinal cells, activate the β - catenin signaling pathway, and promote cell proliferation. The metabolic product of gut microbiota, butyrate, can inhibit histone deacetylase, making it easier for oncogenes to be activated [7]. At the same time, when the imbalance of the microbiota disrupts the intestinal barrier, lipopolysaccharides (LPS) enter the bloodstream, activate the TLR4 pathway, and trigger inflammation. Inflammatory factors also stimulate tumor growth [8].

5. Treatment Strategy Based on Multimodal Omics

After analyzing the molecular mechanisms of colorectal cancer through multimodal omics, targeted and precise treatment strategies can be designed. The molecular features discovered by

multimodal omics can make treatment more precise. The following are two widely used treatment methods: combination therapy and targeted combination therapy. When PI3K inhibitors, P-glycoprotein inhibitors, and glutamine antagonists are used in combination, CB-839 can cause tumor cells to accumulate reactive oxygen species (ROS), and 5-fluorouracil can use ROS to enhance DNA damage. This combination therapy has a stronger inhibitory effect on PIK3CA mutant tumors [6]. BRAF V600E mutant tumors have a high tolerance to BRAF inhibitors (Vimafenib) because inhibiting BRAF may reactivate MEK. However, the combined use of MEK inhibitor (trametinib) can block the upstream and downstream of the MAPK pathway. Vimentinib binds to BRAF, while trametinib binds to MEK, avoiding signal "bypass" transmission. Clinical studies have shown that this combination therapy can increase the objective response rate of patients from 15% to 40% [4].

6. Clinical Application of Multimodal Omics Combined with Biomarkers

6.1. Complementary Detection of Plasma and Fecal Metabolites

Oleic acid and dehydrocholic acid in plasma can reflect the metabolic status of tumors. When the oleic acid content is high and the dehydrocholic acid content is low, the PI3K/Akt pathway becomes more active and the tumor growth rate accelerates. Metabolites of gut microbiota (deoxycholic acid salts) can be detected in excreta and are "products" of Clostridium nucleatum, which can reflect imbalances in gut microbiota [10]. The combined detection of plasma and fecal markers can increase the detection rate of early colorectal cancer and precancerous polyps to 43%, and is more easily accepted by patients compared to traditional colonoscopy screening [2].

6.2. Joint Analysis of Microbiome and Host Genes

By detecting the levels of Fusobacterium nucleatum and Porphyromonas in excreta, and combining with the presence of APC gene mutations in patients, a diagnostic model can be constructed, with an accuracy (AUC value) of 0.9 [7]. At the same time, DNA of Porphyromonas gingivalis can be detected in the excrement of colorectal cancer patients. If it is detected in combination with plasma CEA, the early misdiagnosis rate can be reduced to 20%.

7. Conclusion

Multi-omics technology systematically analyzes the molecular characteristics of CRC and provides multi-dimensions support for accurate cure. Multi-omics has become a crucial method for research and clinical application in this field. This paper reviews the specific applications of multi-omics. Genomics located therapeutic target by recognized driver gene APC and KRAS. Transcriptomics realize tumor classification and drug sensitivity prediction base on RNA expression pattern. Proteomics clarify the biological effects by verify the abnormal activity of PI3K and PD-L1 protein. Metabolomics capture oleic acid and other characteristic metabolites to provide marks for early diagnosis. Microbiomics reveal the mechanism that intestinal flora promotes the development of tumor by metabolites and inflammatory response. At the same time, the integration of causal chains from multi-omics data (Genome→Transcriptome→Proteome→Metabolome) provide theoretical foundation for drug combination strategies (PI3K inhibitor + glutamine antagonist). And the combined detection of plasma and fecal markers increase the efficiency of clinical diagnosis. Those discovers deepen the recognize of CRC pathogenesis and promote the shift of cure from "experience-based medicine" to "Precision medicine". There are lot of limitation of research now. The standardized flow of integration of multi-omics data is not complete. Tumor heterogeneity and detection cost imitated the technology popularization. In the future, we can use artificial intelligence to reinforce the cross-omics data analysis and combine the single-cell sequencing technology to refining characteristic of molecules.

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