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Dietary Fiber–Gut Microbiota Axis Improves Colorectal Tumor Immunity via HCAR2 Activation and HDAC Inhibition: A Bioinformatics Analysis

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Abstract. Tumor immunotherapy has made a breakthrough in cancer treatment, but its efficacy is generally restricted by the tumor's immune microenvironment. The aim of this study is to systematically explain the mechanism of dietary fiber in improving the tumor immune microenvironment by regulating intestinal flora, and for the first time, integrate multi-dimensional bioinformatics methods to systematically verify the key targets of the dietary fiber-SCFAs axis, the butyrate receptor HCAR2 and the epigenetic target HDAC1/2/3. Studies have found that the expression of HCAR2 is up-regulated in colorectal cancer, and its high expression is closely related to the prolonged overall survival and enhanced CD8+ T cell infiltration. The high expression of HDAC1/2/3 is positively correlated with the infiltration of immunosuppressive cells, suggesting that the dietary fiber-SCFAs axis may regulate anti-tumor immunity through the dual mechanism of synergistically activating HCAR2 and inhibiting HDACs. Notably, the effect was cancer species-specific, and the same pattern was not observed in gastric and liver cancers. This study has shown that increasing dietary fiber intake may improve the immune microenvironment of colorectal cancer by specifically activating the HCAR2 pathway, which provides a theoretical basis and translational direction for precision immunity strategies based on nutritional intervention.

Keywords: Dietary fiber, Short-chain fatty acids, Tumor microenvironment, Immune regulation, Bioinformatics.

1. Introduction

The efficacy of tumor immunotherapy is generally limited by the immunosuppressive microenvironment, and the overall response rate is less than 30% [1,2]. In recent years, the role of "gut-tumor axis" in the regulation of tumor immunity has attracted much attention, especially short-chain fatty acids (SCFAs) produced by intestinal flora metabolizing dietary fiber, which are considered to have important immunomodulatory functions [3]. Although existing research evidence shows that high dietary fiber intake is associated with prolonged survival in patients with colorectal cancer [4] and improved immunotherapy response in patients with melanoma [5], the targets of

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SCFAs in human tumor tissues (including specific receptors and epigenetic regulators) remain insufficiently validated in systematic studies. The gap seriously limits the accurate translation of relevant nutritional intervention strategies.

To fill this critical gap, this study systematically analyzed the regulatory mechanism of the "dietary fiber-SCFAs axis" in improving tumor microenvironment immunity. In addition, bioinformatics methods were used to verify the key targets in the SCFAs signaling pathway for the first time. By integrating bioinformatics platforms such as GEPIA2 and TIMER, SCFAS-related immunomodulatory targets were systematically verified from multiple perspectives such as expression differences, survival prognosis and immune infiltration. Including the significance of its specific receptors (HCAR2, FFAR2, FFAR3), epigenetic regulatory targets (HDAC1/2/3) and key immune cell markers (CD8A, FOXP3, CD68).

Studies have revealed the specific expression pattern of these targets in COAD and their significant association with patient prognosis. This study not only provides bioinformatics evidence for the regulatory axis of "dietary fiber-SCFAS-immune microenvironment", but also establishes a data-driven analysis framework for nutritional immune targets. It provides a new perspective and methodological basis for the development of precise dietary-immune combined treatment strategies in the future.

2. Interactions among dietary fiber, gut microbiota, and metabolites

The efficacy of tumor immunotherapy is highly restricted by the immunosuppressive tumor microenvironment (TME) [6]. In recent years, studies have revealed a concept, the "gut-tumor axis", indicating that the distal gut microbiota can systematically modulate anti-tumor immunity [3]. Within this framework, dietary fiber, as a key dietary intervention factor, serves as a bridge connecting nutrition and immunity by shaping intestinal flora and then affecting the production of its metabolites [7].

2.1. Types of dietary fiber and microbial fermentation

Dietary fiber is mainly divided into soluble (e.g., glycans and resistant starches) and insoluble (e.g., cellulose) [8]. As prebiotics, they can selectively promote the proliferation of beneficial bacteria, such as Bifidobacterium and Akkermansia, and maintain the diversity and stability of intestinal microecology [9]. This process is not only a simple change in the composition of the microbiota, but also the first step to activate the downstream immunomodulatory effect [10].

2.2. Generation, absorption and systemic circulation of SCFAs

Intestinal flora fermentates dietary fiber to produce a series of short-chain fatty acids (SCFAs), mainly including acetate, propionate and butyrate [11]. After absorption by intestinal epithelial cells, some of these SCFAs provide energy for the intestine, and the other part enters the portal circulation, thereby exerting systemic immunomodulatory functions [12]. Among them, butyrate is regarded as the core effector molecule in this pathway because of its prominent role in epigenetic regulation and anti-inflammation [13,14].

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3. Microbial metabolites (SCFAs) reshape the immune mechanism of the tumor microenvironment

SCFAs remodel the TME through a multi-dimensional and synergistic mechanism. Its function integrates multiple biological roles such as energy supply, signal transduction and epigenetic regulation to jointly regulate the function of immune cells (Figure 1).

3.1. Signaling to immune cells via g protein-coupled receptors

SCFAs are the natural ligands of a variety of G protein-coupled receptors (GPCRs) [15]. Butyrate specifically activates HCAR2, while propionate and acetate mainly activate free fatty acid receptors 2 and 3 (FFAR2/3) [15]. These receptors are widely expressed on the surface of a variety of immune cells such as T cells, macrophages, dendritic cells and so on [15]. Receptor activation can not only regulate the secretion of key cytokines such as IL-10 and IFN-γ, affect the differentiation and function of immune cells, but also directly enhance the body's anti-tumor immune response or inhibit the immunosuppressive activity, thus playing an important regulatory role in the tumor immune microenvironment [16].

3.2. Inhibiting the epigenetic target HDAC restructures the function of immune cells

The intestinal microbial metabolite butyrate is an effective histone deacetylase (HDAC) inhibitor, specifically inhibiting the activities of HDAC1, HDAC2, and HDAC3 [17]. This inhibitory effect leads to the relaxation of chromatin structure and subsequently upregulates the transcription of key immune regulatory genes such as IFNG and TNF [18]. This epigenetic reprogramming directly enhances the cytotoxic functions of CD8+ T cells and natural killer (NK) cells, while weakening the immunosuppressive phenotype of regulatory T cells (Tregs) [18]. In summary, the HDAC inhibition mediated by butyrate can reverse the immunosuppressive state of the tumor microenvironment at the epigenetic level.

3.3. SCFAs serve as a metabolic intervention to optimize the function and survival of immune cells

In the highly competitive and acidic tumor microenvironment, short-chain fatty acids (SCFAs) can serve as an alternative energy source for infiltrating immune cells [19]. More importantly, they drive metabolic reprogramming in T cells by activating AMP-activated protein kinase (AMPK) [20]. This metabolic adaptation optimizes the energy utilization efficiency of T cells, ultimately enhancing their survival ability in the tumor microenvironment and maintaining their long-term immune surveillance function.

3.4. SCFAs combined with immune checkpoint inhibitors can synergistically reverse immune therapy resistance

The combined effect of the above mechanisms can promote the transformation of the tumor microenvironment from an immunosuppressive type to an immunostimulatory type. This is manifested by an increase in the infiltration of cytotoxic T cells and a weakening of the functions of immunosuppressive cells, enabling SCFAs to have a significant synergistic effect with immune checkpoint inhibitors such as PD-1/PD-L1, providing a highly promising combined strategy for overcoming immune therapy resistance [21].

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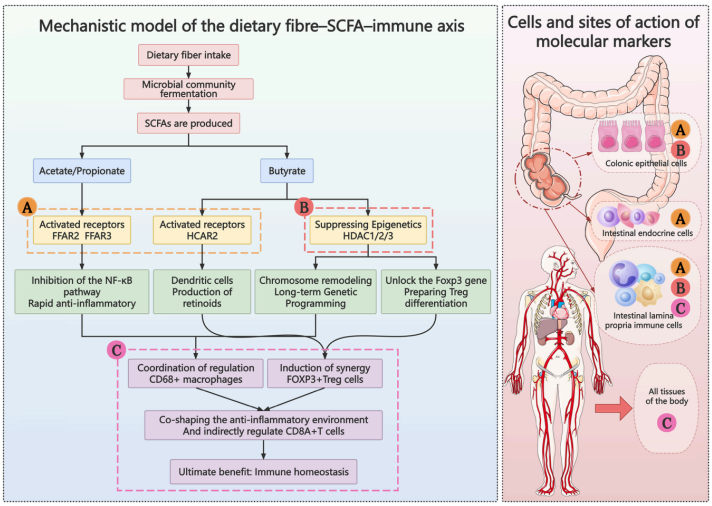

Figure 1. Mechanistic diagram: dietary fiber modulates the tumor immune microenvironment via gut microbiota metabolism (picture credit: original)

4. Bioinformatics validation and model support for key immunomodulatory targets

Although the mechanism research has been in-depth, translating these findings from basic science to clinical practice requires strong support from human data. This study is the first to adopt bioinformatics methods to systematically validate the core targets in the above-mentioned mechanism.

4.1. The expression of SCFAs receptors and its correlation with prognosis analysis

This study utilized platforms such as GEPIA2 and TIMER2.0, based on large clinical cohort data from TCGA, for analysis (Figure 2). The results showed that in colorectal cancer (COAD), the expression of HCAR2 exhibited significant tissue specificity, and its high expression was closely related to the prolonged overall survival (OS) of patients. Additionally, in the tumor tissues of the HCAR2 high-expression group, the infiltration level of CD8+ T cells was significantly higher. This provided strong clinical relevance evidence for the hypothesis that "HCAR2 signaling enhances anti-tumor immunity".

4.2. Analysis of the expression of epigenetic targets (HDACs) and immune infiltration

The analysis of the epigenetic target HDAC1/2/3 revealed an additional dimension of this mechanism: its high expression is often positively correlated with the infiltration degree of immunosuppressive cells (such as regulatory T cells, M2-type macrophages), and is associated with a poorer prognosis. This finding is highly consistent with the theoretical model of "butyrate alleviates immunosuppression by inhibiting histone deacetylases (HDACs)" [22]. Figure 2 shows the manifestation of genes in digestive tract tumors.

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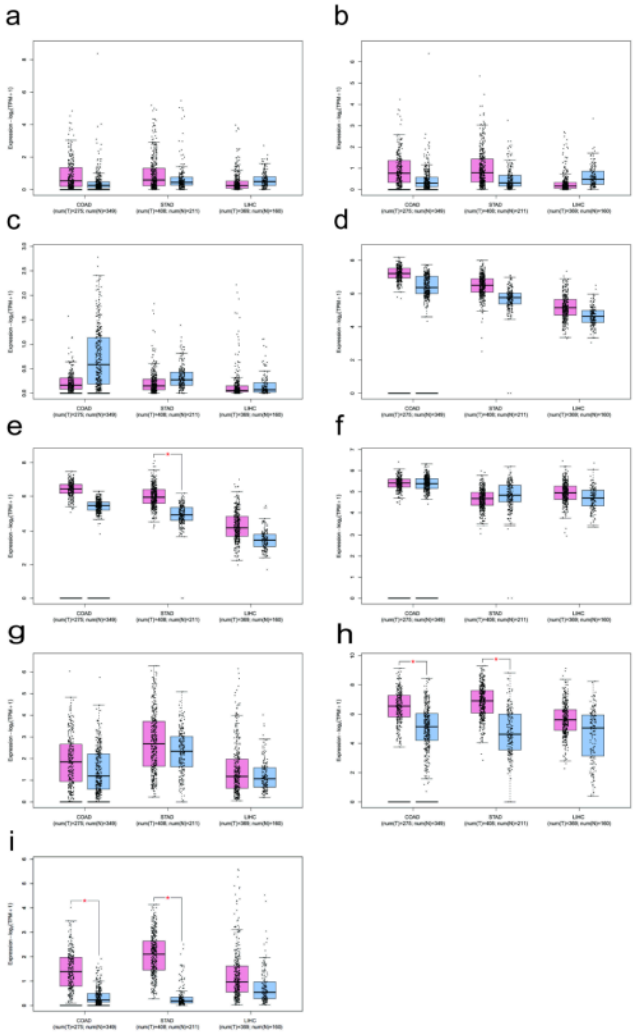

Figure 2. The expression profile of key target genes in the dietary fiber-SCFAs axis. a. HCAR2 b. FFAR2 c. FFAR3 d. HDAC1 e. HDAC2 f. HDAC3 g. CD8A h. CD68 i. FOXP3 (picture credit: original)

4.3. The potential pathways revealed by the joint analysis

Further gene set enrichment analysis (GSEA) revealed that in tumor samples with high expression of HCAR2, key immune pathways such as the T-cell receptor signaling pathway and the interferon-γ response were significantly activated (Figure 3). This constructed a complete "target - immune pathway - clinical prognosis" correlation network at the data level, systematically verifying the potential action pathway of the dietary fiber-SCFAs axis.

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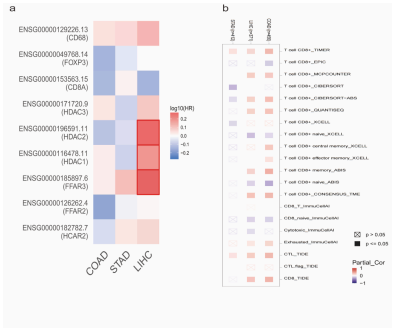

Figure 3. Multidimensional analysis of prognostic risks associated with immune-related genes and characteristics of immune cell infiltration. a is prognostic risk ratio heat map of immune-related genes in different digestive tract tumors. b is heatmap showing the partial correlation and significance of immune cell infiltration and related markers. (picture credit: original)

4.4. Supporting evidence for the mechanism model: insights from animal experiments

The animal models provided crucial causal evidence for this bioinformatics discovery. The study confirmed that dietary fiber or intervention with direct supplementation of butyrate could significantly inhibit tumor growth in mice and enhance anti-tumor immunity; however, in the mouse model with Gpr109a gene knockout (encoding the mouse homolog of the human HCAR2 receptor), the protective effect was significantly weakened [23]. This result indicates that GPR109A/HCAR2 is a crucial molecule indispensable for mediating the immunomodulatory function of butyrate [23]. However, it must be noted that there are differences in the microbiota, metabolism, and immune microenvironment among species. Therefore, the effectiveness and universality of this mechanism in humans still need to be ultimately verified through prospective clinical studies.

5. Conclusion

This review systematically elaborates on the crucial role and molecular mechanisms of the "dietary fiber - gut microbiota - short-chain fatty acids (SCFAs)" axis in reshaping the tumor immune microenvironment. Based on the existing evidence and bioinformatics analysis, this study confirmed that short-chain fatty acids (particularly butyrate) activate the HCAR2 receptor through a dual pathway and inhibit the activities of HDAC1/2/3. This plays a central role in regulating the functions of immune cells and their epigenetic states, and at the same time provides a mechanistic basis for the immune regulatory effects of dietary fibers.

This study is the first to conduct multi-dimensional bioinformatics validation using public databases. It was found that in colorectal cancer, high expression of HCAR2 is associated with prolonged patient survival and enhanced infiltration of $CD8^+$ T cells, while high expression of HDAC1/2/3 is positively correlated with an immunosuppressive microenvironment. This provides key targets and principal evidence for the "dietary fiber-SCFAs-immune microenvironment" axis. It should be noted that this study aims to reveal the potential biological significance of the HCAR2 pathway. Although it has gained causal support from animal experiments, its clinical effectiveness and universality in humans still need to be further verified by prospective studies.

Based on the above findings and limitations, future research should focus on conducting prospective clinical intervention trials to systematically evaluate the impact of dietary fiber on the expression of patient targets and immune responses; utilize molecules such as HCAR2 to identify potential target populations that may respond effectively to dietary fiber intervention, promoting the

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clinical translation of personalized nutrition strategies; deeply explore the synergistic effect of dietary fiber and immunotherapy, and develop new "diet-drug" combined treatment strategies.

By promoting these studies, this paper hope to transform dietary fiber from a general health recommendation into a precise and effective adjunctive treatment method for tumors.

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