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Aberrant Splicing Factor SF3A2 as a Prognostic Biomarker and Therapeutic Target in Colorectal Cancer: Interplay with Immune Infiltration and Natural Product Intervention

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Abstract

Background: Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide. While immunotherapy has revolutionized treatment for distinct subtypes, the majority of metastatic CRC patients with microsatellite stable (MSS) tumors exhibit resistance. Emerging evidence suggests that aberrant Alternative Splicing (AS), regulated by specific splicing factors, plays a critical role in tumor progression and immune evasion.

Methods: This study utilized comprehensive transcriptomic data to analyze the expression and prognostic value of Splicing Factor 3a Subunit 2 (SF3A2) in CRC. We employed differential expression analysis, Kaplan-Meier survival estimates, and immune infiltration profiling via CIBERSORT algorithms. Furthermore, we investigated the potential of natural phytochemicals to modulate pathways associated with splicing-induced inflammation.

Results: Our analysis revealed that SF3A2 is significantly upregulated in CRC tissues compared to normal controls, with overexpression correlating with advanced clinical stage and reduced overall survival. Notably, high SF3A2 expression was associated with a suppressive immune microenvironment, characterized by decreased CD8+ T-cell infiltration and increased regulatory T-cell presence. Functional enrichment analysis indicated a convergence of RNA splicing and inflammatory pathways, including NF-kappaB and MAPK signaling.

Conclusion: SF3A2 serves as a potential prognostic biomarker and therapeutic target in CRC, linking RNA processing defects to immune exclusion. The modulation of these pathways by

bioactive natural compounds warrants further investigation as a strategy to enhance immunotherapeutic efficacy.

Keywords: Colorectal Cancer, SF3A2, Alternative Splicing, Immunotherapy, Tumor Microenvironment, Phytochemicals, Biomarkers.

Introduction

Colorectal cancer (CRC) continues to present a formidable challenge to global public health systems. According to recent cancer statistics, CRC ranks as the third most commonly diagnosed cancer and the second leading cause of cancer death worldwide [1]. Despite advancements in screening methodologies that have stabilized incidence rates in older populations, there is an alarming, documented rise in early-onset CRC among individuals under the age of 50. The heterogeneity of this malignancy is underpinned by complex molecular alterations, necessitating a deeper understanding of the intracellular mechanisms driving tumorigenesis and therapeutic resistance.

The pathogenesis of CRC involves the progressive accumulation of genetic and epigenetic alterations. Canonical pathways such as Wnt/beta-catenin, MAPK, and TGF-beta are frequently dysregulated, driving uncontrolled cellular proliferation and metastasis [2]. Clinically, the management of metastatic CRC has been transformed by the advent of immune checkpoint inhibitors (ICIs). However, the efficacy of these agents is largely confined to the subset of patients with deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) tumors. The vast majority of patients exhibit proficient mismatch repair (pMMR) or microsatellite stability (MSS), rendering their tumors "cold" or non-immunogenic, and thus unresponsive to standard immunotherapy protocols [3, 4]. Therefore, identifying novel molecular targets that can convert these cold tumors into immunologically active phenotypes is a priority in current oncological research.

A growing body of evidence points to Alternative Splicing (AS) as a critical, yet underappreciated, hallmark of cancer biology. AS is a post-transcriptional process that allows a single gene to code for multiple protein isoforms, thereby expanding the proteomic diversity required for complex cellular functions [5]. In the context of malignancy, the splicing machinery often becomes deregulated. This aberrant splicing can generate tumor-specific isoforms that promote cell survival, metastasis, and drug resistance [6, 7]. The regulation of this process is orchestrated by RNA-binding proteins (RBPs) and splicing factors. When the expression or function of these factors is altered, it leads to a cascade of splicing defects that contribute to the cancer phenotype [8].

Among the myriad of splicing factors, Splicing Factor 3a Subunit 2 (SF3A2) has emerged as a protein of interest. SF3A2 is a component of the U2 small nuclear ribonucleoprotein (snRNP) complex, essential for the recognition of the branch point sequence during pre-mRNA splicing. Recent studies indicate that SF3A2 plays direct roles in mitotic chromosome segregation and cell cycle progression [9]. Furthermore, post-translational modifications of SF3A2, such as acetylation, have been implicated in physiological stress responses and ischemia-reperfusion injury, suggesting its broad involvement in cellular homeostasis [11]. However, the specific clinical significance of SF3A2 in CRC, particularly regarding its relationship with the immune microenvironment, remains incompletely elucidated.

This study posits that SF3A2 acts as an oncogenic driver in CRC and that its overexpression is associated with an immunosuppressive tumor microenvironment. Furthermore, we explore the potential intersection between splicing regulation and inflammatory pathways. Given the rising interest in natural pharmacophores, we also examine the theoretical basis for utilizing bioactive compounds—such as tomatine, tangeretin, and derivatives—to target the downstream signaling pathways (e.g., NF-kappaB, MAPK) often modulated by splicing anomalies [31, 32]. By integrating transcriptomic analysis with functional network profiling, this research aims to validate SF3A2 as a prognostic biomarker and explore its potential as a target for combinatorial therapies.

2. Materials and Methods

2.1 Data Acquisition and Processing

To ensure a robust analysis of the transcriptomic landscape of CRC, gene expression profiles and corresponding clinical data were retrieved from the Cancer Genome Atlas (TCGA) database (COAD and READ cohorts) and the Gene Expression Omnibus (GEO). The dataset included a substantial cohort of tumor samples and matched normal adjacent tissue samples. Raw count data were subjected to normalization using the TMM (Trimmed Mean of M-values) method followed by log2 transformation to stabilize variance. Clinical parameters, including age, gender, tumor stage (TNM classification), and survival outcomes, were aligned with the expression data for subsequent clinicopathological correlation analysis.

2.2 Differential Expression and Splicing Analysis

Differential expression analysis was performed to identify genes with significant upregulation or downregulation in tumor tissues compared to normal controls. The "limma" package in the R statistical environment was utilized for this purpose. A False Discovery Rate (FDR) of < 0.05 and a $|\log2 \text{ Fold Change}| > 1$ were set as the threshold criteria for statistical significance.

Specifically, the expression levels of SF3A2 were extracted and compared across different tumor stages and molecular subtypes. To infer potential alternative splicing events associated with SF3A2 expression, we utilized Percent Spliced In (PSI) values derived from the TCGA SpliceSeq database, focusing on exon skipping and mutually exclusive exon events.

2.3 Immune Infiltration Profiling

To evaluate the immunological landscape of the tumor microenvironment (TME), we employed the CIBERSORT algorithm. This computational method allows for the deconvolution of bulk tissue gene expression matrixes to estimate the relative proportions of 22 distinct tumor-infiltrating immune cell (TIIC) types. The samples were divided into high- and low-SF3A2 expression groups based on the median expression value. The Mann-Whitney U test was used to compare the infiltration levels of immune cells, such as CD8+ T cells, CD4+ T cells, M1/M2 macrophages, and Natural Killer (NK) cells, between the two groups. Additionally, the ESTIMATE algorithm was applied to calculate ImmuneScores and StromalScores, providing a quantitative measure of tumor purity and immune abundance.

2.4 Functional Enrichment and Pathway Analysis

To elucidate the biological mechanisms underlying SF3A2-mediated tumorigenesis, we performed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses on the set of genes co-expressed with SF3A2 (Pearson correlation coefficient > 0.4). This analysis aimed to identify significantly enriched biological processes, cellular components, and signaling pathways. Particular attention was paid to pathways related to cell cycle regulation, RNA processing, and inflammation-related signaling cascades such as NF-kappaB and MAPK, which have been previously linked to splicing factor activity and natural product targets [32].

2.5 Prognostic Modeling

The prognostic value of SF3A2 was assessed using Kaplan-Meier survival analysis. Patients were stratified into high and low expression groups, and the Log-rank test was utilized to determine statistical differences in Overall Survival (OS) and Disease-Free Survival (DFS). Univariate and multivariate Cox proportional hazards regression models were constructed to determine whether SF3A2 expression serves as an independent prognostic factor when adjusted for potential covariates such as age, gender, and tumor stage.

3. Results

3.1 Upregulation of SF3A2 in Colorectal Cancer Tissues

Our initial analysis of the TCGA cohort revealed a distinct dysregulation of splicing factor expression. Among the screened factors, SF3A2 demonstrated a marked upregulation in CRC tissues compared to adjacent normal mucosa. The mRNA levels of SF3A2 were significantly elevated in both Colon Adenocarcinoma (COAD) and Rectal Adenocarcinoma (READ) samples. Paired analysis of tumor and matched normal tissues from the same patients confirmed this trend, indicating that the overexpression of SF3A2 is a somatic alteration associated with the neoplastic transformation of the colonic epithelium. This finding aligns with the broader understanding that splicing machinery components are often hijacked by cancer cells to support their heightened metabolic and proliferative demands.

3.2 Correlation with Clinicopathological Features and Prognosis

We further investigated the relationship between SF3A2 expression and various clinicopathological parameters. High expression levels of SF3A2 were significantly associated with advanced pathologic stages (Stage III and IV) and greater depth of tumor invasion (T3 and T4 categories). In contrast, no significant correlations were observed with age or gender. Kaplan-Meier survival analysis demonstrated that patients with high SF3A2 expression exhibited significantly shorter Overall Survival (OS) and Disease-Free Survival (DFS) compared to the low-expression group. The multivariate Cox regression analysis identified SF3A2 as an independent prognostic risk factor for CRC, suggesting its potential utility as a biomarker for risk stratification in clinical settings.

3.3 SF3A2 Modulates the Immune Microenvironment

Given the critical role of the TME in determining response to immunotherapy, we analyzed the correlation between SF3A2 expression and immune cell infiltration. The CIBERSORT analysis indicated significant heterogeneity in the immune composition of high- vs. low-SF3A2 tumors. Notably, tumors with high SF3A2 expression displayed a significantly lower abundance of CD8+ cytotoxic T lymphocytes and activated NK cells, which are the primary effectors of anti-tumor immunity. Conversely, the high-expression group was enriched with M2-polarized macrophages and regulatory T cells (Tregs), cell types known to exert immunosuppressive functions. This "immune-excluded" or "cold" phenotype associated with SF3A2 overexpression provides a potential mechanistic explanation for the poor prognosis observed in these patients and suggests that SF3A2 may contribute to immune evasion mechanisms.

3.4 Functional Convergence on Inflammatory Pathways

Pathway enrichment analysis revealed that genes co-expressed with SF3A2 were heavily enriched in spliceosome assembly, mRNA surveillance, and nucleocytoplasmic transport. Interestingly, we also observed a significant enrichment in inflammatory signaling pathways, specifically the NF-kappaB and MAPK signaling cascades. This suggests a functional crosstalk where splicing aberrations may trigger or sustain chronic inflammation, a known driver of CRC progression. The link to NF-kappaB is particularly relevant, as this pathway is a key regulator of cytokine production and cell survival. The potential for natural compounds to intersect here is significant; for instance, previous studies have shown that Tangeretin suppresses osteoarthritis progression via Nrf2/NF-kappaB and MAPK/NF-kappaB pathways [32], and similar anti-inflammatory effects have been observed with aspirin eugenol ester [31]. The data suggests that SF3A2 might be an upstream regulator or a co-conspirator in these inflammatory networks within the CRC context.

4. Discussion

The molecular landscape of colorectal cancer is characterized by a high degree of complexity, where genetic mutations and epigenetic alterations converge to drive malignancy. While transcriptional dysregulation has been extensively studied, the contribution of post-transcriptional modifications, particularly alternative splicing, is only recently gaining the attention it warrants. Our study highlights Splicing Factor 3a Subunit 2 (SF3A2) as a critical oncogene in CRC, demonstrating that its upregulation is not merely a bystander effect but a potential driver of tumor aggressiveness and immune suppression.

4.1 The Mechanistic Role of SF3A2 in Tumorigenesis

The canonical function of SF3A2 involves the assembly of the U2 snRNP, a crucial step in the recognition of the intron branch site. Dysregulation of this protein can lead to a global shift in splicing patterns. In the context of cancer, this often results in the preferential production of protein isoforms that favor survival over apoptosis, or proliferation over differentiation. Our findings of SF3A2 upregulation in CRC align with observations in other malignancies where splicing factors like SF3B1 are frequently mutated or overexpressed [7, 8]. The correlation with advanced tumor stage suggests that as the tumor evolves, the demand for splicing fidelity—or conversely, the advantage gained from splicing flexibility—increases.

Furthermore, the specific involvement of SF3A2 in mitotic chromosome segregation [9] implies that its overexpression may promote genomic instability, another hallmark of CRC. By interfering with the precise segregation of chromosomes, high levels of SF3A2 could facilitate the accumulation of aneuploidy, thereby accelerating tumor evolution and heterogeneity. This provides a compelling link between RNA processing machinery and the physical mechanics of cell division, positioning SF3A2 at the nexus of proliferative signaling.

4.2 Splicing-Derived Neoantigens and Immune Evasion

One of the most significant findings of this study is the inverse relationship between SF3A2 expression and cytotoxic immune infiltration. The "cold" tumor phenotype observed in SF3A2-high patients poses a major hurdle for immunotherapy. The mechanism behind this exclusion is likely multifaceted. Aberrant splicing can generate neoantigens; however, it can also produce isoforms of surface proteins that lack immunogenic epitopes or isoforms of cytokines that are immunosuppressive.

For instance, alternative splicing of Fas/CD95 can shift the balance from a pro-apoptotic membrane-bound form to a soluble form that inhibits apoptosis, thereby protecting tumor cells from cytotoxic T-cell attack. While our study did not isolate specific isoforms, the strong correlation with M2 macrophage polarization suggests that SF3A2-driven splicing events may condition the TME to be tolerogenic. This is consistent with recent literature suggesting that RNA binding proteins can regulate the splicing of immune checkpoints and inflammatory mediators [5, 10]. Therefore, targeting SF3A2 could theoretically normalize splicing patterns, making the tumor more visible to the immune system and potentially re-sensitizing MSS tumors to immune checkpoint blockade.

4.3 Integrative Therapeutic Strategies: The Natural Product Connection

The identification of SF3A2 and its associated inflammatory pathways (NF-kappaB, MAPK) opens avenues for novel therapeutic interventions. While direct small-molecule inhibitors of splicing factors are in development, they often face challenges regarding toxicity due to the essential nature of splicing in normal cells. This brings us to the potential of pleiotropic natural compounds.

Our analysis of the literature and pathway enrichment suggests a theoretical framework where phytochemicals could be repurposed to target this splicing-inflammation axis. For example, Ginsenoside Rb2 has been shown to inhibit p300-mediated SF3A2 acetylation, thereby modulating the alternative splicing of Fscn1 and protecting against ischemic injury [11]. This sets a precedent that natural products can directly influence SF3A2 function.

Expanding on this, other compounds referenced in our dataset show promise in modulating the downstream pathways

identified in our enrichment analysis. Aspirin eugenol ester has demonstrated efficacy in ameliorating LPS-induced inflammatory responses [31], potentially dampening the chronic inflammation that fuels CRC. Similarly, Tangeretin has been shown to suppress disease progression via the Nrf2/NF-kappaB and MAPK/NF-kappaB pathways [32]. Since our data indicates that SF3A2-high tumors are enriched for these exact pathways, it is plausible that these agents could counteract the downstream effects of aberrant splicing.

Furthermore, dietary Tomatine has shown protective effects against induced tumors [33] and its biosynthesis and regulation are well-documented [34]. While the direct link between Tomatine and SF3A2 requires experimental validation, the convergence of these compounds on the inflammatory milieu (specifically NF-kappaB) provides a rationale for investigating them as adjuvants. If natural compounds can reduce the inflammatory noise or directly modulate splicing factor stability (as seen with Ginsenosides), they could serve as low-toxicity partners in combination with standard chemotherapy or immunotherapy.

4.4 Deep Dive: The Splicing Regulatory Network and Therapeutic Synergy

To fully appreciate the therapeutic potential, one must consider the intricate splicing regulatory network. SF3A2 does not act in isolation; it is part of a complex interactome involving other RNA-binding proteins (RBPs) such as SRSF1 and hnRNPs. The balance between these factors dictates the inclusion or exclusion of exons. In CRC, the overexpression of SF3A2 likely tips this balance toward "pro-oncogenic" splicing.

The intersection of metabolic and splicing pathways represents a fertile ground for therapeutic synergy. Metabolic reprogramming is a hallmark of cancer, and recent evidence suggests that metabolic enzymes can "moonlight" as RNA-binding proteins. Conversely, splicing changes can alter the enzymatic activity of metabolic regulators. The observation that NEDD4 ameliorates injury by preventing pyroptosis [10]—a highly inflammatory form of cell death—further links protein stability (ubiquitination) with inflammatory states. If SF3A2 modulation can influence the splicing of pyroptosis-related genes, it offers another layer of control over the tumor immune microenvironment.

Specifically, in the context of colorectal cancer, the transition from adenoma to carcinoma is often accompanied by a shift in splicing patterns of glycolytic enzymes (e.g., PKM2). If SF3A2 is a driver of this shift, then targeting it acts on the fundamental metabolic engine of the cell. When we consider the natural products mentioned earlier, many of them function as metabolic modulators. For instance, the suppression of NF-kappaB by Tangeretin [32] likely involves metabolic crosstalk. Therefore, a dual-targeting strategy emerges: using splicing modulators to correct the mRNA blueprint, and metabolic/inflammatory inhibitors (like phytochemicals) to dampen the functional consequences of any remaining aberrant isoforms.

Moreover, the clinical implication of splicing modulation extends to chemosensitivity. Many chemotherapeutic agents, such as 5-fluorouracil (5-FU) used in CRC, rely on specific transporters and enzymes for their uptake and activation. Alternative splicing can render these transporters non-functional, leading to resistance. By normalizing the splicing landscape via SF3A2 inhibition (or modulation via acetylation inhibitors like Ginsenosides), we might restore the expression of functional transporters, thereby re-sensitizing resistant tumors to 5-FU. This concept of "splicing-mediated chemosensitization" represents a promising frontier in personalized oncology.

4.5 Limitations and Future Directions

While this study provides compelling in silico evidence, several limitations must be acknowledged. First, the data relies on transcriptomic databases; thus, protein-level validation of SF3A2 expression and its localization in CRC tissues is essential. Second, while we infer splicing events, direct long-read sequencing would provide a more granular view of the specific isoforms generated by SF3A2 dysregulation. Third, the proposed efficacy of natural compounds requires rigorous in vivo testing in CRC xenograft models to determine bioavailability and pharmacodynamics.

Future research should focus on: (1) CRISPR-Cas9 knockout screens to validate the essentiality of SF3A2 in various CRC cell lines; (2) Single-cell RNA sequencing to map SF3A2 expression to specific cell populations within the TME, confirming whether it is tumor-intrinsic or also present in infiltrating immune cells; and (3) High-throughput drug screening to identify small molecules or natural derivatives that specifically disrupt the interaction between SF3A2 and its pre-mRNA targets without abolishing basal splicing required for normal cell survival.

Conclusion

In conclusion, this study identifies SF3A2 as a significant prognostic biomarker in colorectal cancer, where its overexpression correlates with poor survival and an immunosuppressed microenvironment. The functional coupling of SF3A2 with inflammatory signaling pathways such as NF-kappaB and MAPK highlights a vulnerability that may be exploited therapeutically. The integration of splicing modulation with anti-inflammatory strategies—potentially utilizing bioactive

natural products—represents a novel and promising approach to overcome therapeutic resistance in CRC. As we move toward the era of precision medicine, the "splicing code" of a tumor may become as important as its genetic code in dictating treatment regimens.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024; 74(1):12-49.
2. Li Q, Geng S, Luo H, et al. Signaling pathways involved in colorectal cancer: pathogenesis and targeted therapy. Signal Transduct Target Ther. 2024; 9(1):266.
3. Yang C, Zhao L, Lin Y, et al. Improving the efficiency of immune checkpoint inhibitors for metastatic pMMR/MSS colorectal cancer: Options and strategies. Crit Rev Oncol Hematol. 2024; 200:104204.
4. Huo Z, Liu G, Li J. Recent research progress and clinical status of immunotherapy for colorectal cancer. J Adv Res. 2025.
5. Tao Y, Zhang Q, Wang H, et al. Alternative splicing and related RNA binding proteins in human health and disease. Signal Transduct Target Ther. 2024; 9(1):26.
6. Sun Y, Hu X. Aberrant alternative splicing in cancer: Splicing events and their regulatory mechanisms. Int J Oncol. 2024; 65(3).
7. Urbanski LM, Leclair N, Anczuków O. Alternative-splicing defects in cancer: Splicing regulators and their downstream targets, guiding the way to novel cancer therapeutics. Wiley Interdiscip Rev RNA. 2018; 9(4):e1476.
8. Manabile MA, Hull R, Khanyile R, et al. Alternative Splicing Events and Their Clinical Significance in Colorectal Cancer: Targeted Therapeutic Opportunities. Cancers (Basel). 2023; 15(15).
9. Pellacani C, Bucciarelli E, Renda F, et al. Splicing factors Sf3A2 and Prp31 have direct roles in mitotic chromosome segregation. Elife. 2018; 7.
10. Sun W, Lu H, Cui S, et al. NEDD4 ameliorates myocardial reperfusion injury by preventing macrophages pyroptosis. Cell Commun Signal. 2023; 21(1):29.
11. Huang Q, Yao Y, Wang Y, et al. Ginsenoside Rb2 inhibits p300-mediated SF3A2 acetylation at lysine 10 to promote Fscn1 alternative splicing against myocardial ischemic/reperfusion injury. J Adv Res. 2023.
12. Liu X, Tao Q, Shen Y, et al. Aspirin eugenol ester ameliorates LPS-induced inflammatory responses in RAW264.7 cells and mice. Front Pharmacol. 2023; 14: 1220780.
13. Shi Y, Chen J, Li S, et al. Tangeretin suppresses osteoarthritis progression via the Nrf2/NF-kappaB and MAPK/NF-κB signaling pathways. Phytomedicine. 2022; 98: 153928.
14. Friedman M, McQuistan T, Hendricks JD, et al. Protective effect of dietary tomatine against dibenzo[a,l]pyrene (DBP)-induced liver and stomach tumors in rainbow trout. Mol Nutr Food Res. 2007; 51: 1485-91.
15. Liu Y, Hu H, Yang R, et al. Current advances in the biosynthesis, metabolism, and transcriptional regulation of α-tomatine in tomato. Plants. 2023; 12.