

Research Progress on Splicing-Factor-Targeted Inhibitors in Hematologic Malignancies

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ABSTRACT

Pre-mRNA splicing is a central regulatory step in eukaryotic gene expression. Splicing factor genes (such as splicing factor 3B subunit 1 [SF3B1], U2 small nuclear RNA auxiliary factor 1 [U2AF1], and serine/arginine-rich splicing factor 2 [SRSF2]) are frequently mutated in hematologic malignancies and have emerged as key oncogenic drivers and highly promising therapeutic targets ^{[1][2]}. In recent years, breakthroughs in cryo-electron microscopy have enabled near-atomic-resolution structural determination of the spliceosome in various functional states ^{[3][4]}, providing precise molecular blueprints for structure-based drug design and fundamentally overturning the long-held view of the spliceosome as an “undruggable” target. This article systematically reviews the structural features, hotspot mutations, and oncogenic mechanisms of the three major splicing factors SF3B1, U2AF1, and SRSF2. It focuses on the development of spliceosome-targeted inhibitors driven by structural biology, including SF3B1-targeting agents (Pladienolide B, E7107, H3B-8800), U2AF1-targeting agents (SF1-8/AP232), SRSF2-targeting strategies (ROCK inhibitors, PRMT5 inhibitors, PARP inhibitors), and inhibitors of the common downstream pathway (IRAK4 inhibitors Emavusertib and R289). The article further analyzes the clinical trial status, core challenges, and future directions for each inhibitor class, aiming to provide a reference for research and clinical practice in this field.

Keywords: Spliceosome; Splicing Factors; SF3B1; U2AF1; SRSF2; Targeted Inhibitors; Hematologic Malignancies

1. INTRODUCTION

Pre-mRNA splicing is a vital post-transcriptional regulatory process in eukaryotic gene expression. Through the excision of introns and ligation of exons, it produces mature mRNA and generates multiple distinct mRNA variants from a single gene, which in turn translate into functionally diverse proteins, greatly expanding proteomic diversity. This intricate process is executed by a dynamic molecular machine called the spliceosome, which is assembled *de novo* on substrate pre-mRNAs from five core small nuclear ribonucleoproteins (snRNPs: U1, U2, U4, U5, and U6) and approximately 100 associated proteins ^[5].

Accumulating evidence indicates that splicing dysregulation is an emerging hallmark of cancer ^[1]. Whole-genome sequencing studies have revealed that splicing factor genes (e.g., SF3B1, U2AF1, and SRSF2) are recurrently mutated in various malignancies, especially hematologic cancers ^{[6][7]}. These mutations cause aberrant splicing of downstream genes, driving tumor initiation, progression, metastasis, and drug resistance. However, the spliceosome has long been considered “undruggable” owing to its structural complexity, dynamic nature, and the apparent lack of well-defined small-molecule binding pockets. This situation has changed greatly with the progress of structural biology, especially cryo-EM. Cryo-EM can now see the various functional states of spliceosome with a fineness close to atom ^{[3][4]}. Now, you can create an accurate “map” for the structure-based drug design. In recent years, inhibitors targeting spliceosome have entered clinical trials, which has become an important step from basic research to clinic.

Based on structural biology, this article aims to organize and review the development and progress of anti-cancer inhibitor aimed at spliceosome. Pay special attention to the structural characteristics, hotspot mutation and development of targeted drugs of SF3B1, U2AF1 and SRSF2, and discuss the current topics and future prospects.

2. FREQUENTLY MUTATED SPLICING FACTORS IN HEMATOLOGIC MALIGNANCIES

2.1 Prevalence and Clinical Significance of Splicing Factor Mutations

In the past ten years, thanks to whole-genome sequencing, we have found several splicing factors, and mutations can be found many times in hematologic malignancies. The most famous is SF3B1, which accounts for 20%~30% in myelodysplastic syndromes (MDS), and more than 80% of MDS with ring sideroblasts has mutation probability. U2AF1 has mutation in about 10% of MDS, and the mutation of SRSF2 can be found in 40%~50% of chronic myelomonocytic leukemia (CMML) [6][7][8]. It can be seen from this skewed distribution that the probability of mutation is much higher than that of ordinary mutation that the mutation of splicing factor is not just there by chance, but the cause of disease (driver events).

Studies have shown that the mutation of splicing factor mostly occurs in the early stage of disease evolution, which may be an opportunity for clonal hematopoiesis and malignant transformation. These mutations affect many important pathways, including DNA damage repair (such as ATM, BRCA1), cell cycle regulation (such as CDC25C), cell apoptosis (such as CASP8, BAX), signal transduction, etc., and eventually lead to cancer [9][10], especially these heterozygous mutations that usually gather in specific hot spots, suggesting that they mainly play a role through negative or acquired mechanisms, rather than complete loss of function [11]. This means that the mutant protein has a unique three-dimensional structure, which may be targeted with low molecular selectivity and become the basis for drug development.

2.2 Association of Splicing Factor Mutations with Clinical Prognosis

The clinical significance of splicing factor mutation in hematological cancer presents a complex pattern in different types of cancer. In MDS, the mutation of SF3B1 is generally related to ring sideroblasts, and the risk of predicting progression to acute myeloid leukemia (AML) is low and the prognosis is good [8]. However, recent studies have found that the mutation of SF3B1 E592K is related to the characteristics of high-risk MDS, such as no ring sideroblasts, increased gemmule and other SF3B1 mutations without good survival advantages [11]. On the contrary, the spliceosome mutation of AML is usually considered as the main reason for poor prognosis [6]. The molecular reasons for these differences in prognosis are not completely clear. The tolerance of cells to each sequence of splicing abnormality may be related to their different co-mutation patterns.

3. STRUCTURAL FEATURES AND HOTSPOT MUTATIONS OF KEY SPLICING FACTORS

3.1 SF3B1: From Core Splicing Factor to Oncogenic Driver

SF3B1 (splicing factor 3B subunit 1) is an important part of U2 snRNP. At the beginning of splicing, find the branch point sequence (BPS) in pre-mRNA to help U2 snRNP stick firmly. So you can put spliceosome in the right place. SF3B1 has 20 HEAT repeats, which are superhelix shaped like riding boots. With SF3B2, SF3B3, SF3B4, SF3B5, SF3B6 and PHF5A, a stable sf3b complex was made [11].

The most well-known hotspot mutation in SF3B1 is K700E. This is the 14th mismatch change of HEAT repeat heterojunction, in which positively charged ricin is replaced by negatively charged glutamic acid. This mutation leads to tumorigenesis through two mechanisms. On the other hand, it destroys the important interaction between SF3B1 and auxiliary protein SUGP1, and prevents SUGP1 from activating the SF1 of helicases branch of DHX15, thus preventing U2 snRNA from correctly pairing with normal BPS. On the other hand, the change of charge causes the change of local shape and the increase of overall softness, which changes the shape of RNA binding surface in a far place and reduces the ability of SF_3b1 to correctly identify branching points in a large range. As a result, the mutant will use the hidden 3' branch point of 10~30 nucleotides upstream of the normal site [11]. This will produce a large number of abnormal mRNA, which contains immature stop codons; Some of them can be eliminated by nonsense, variation, dependence and decomposition, while others are translated into ineffective protein, which eventually causes cancer through downstream channels such as NF κ B, AKT and p53 [9].

The mutation of SF3B1 is not just hematologic tumors. Located in 20%~25% of uveal melanomas, it is also common in breast and pancreatic ductal adenocarcinomas [6]. Because mutations have been found in so many tumors, SF3B1 is expected to be a pan-cancer therapeutic target.

3.2 U2AF1: Recognizer of the 3' Splice Site

U2AF1 is the auxiliary factor of U2 snRNP, which is used to find the 3' splice site of pre-mRNA in early splicing. Protein has two important RNA recognition motifs (RRMs), which are found in AG dinucleotide and polypyrimidine tract near 3' splice site. The structural study shows that U2AF1 and U2AF2 stick together as a heterodimer, and together determine the boundary of splice-site [12].

The hotspot mutation of U2AF1 is clustered in S34 and Q157 of two RRM domains. Among the most S34F mutations, serine will be replaced by phenylalanine, thus changing the preference of RNA sequence of RRM. In particular, the mutant U2AF1 will change the recognition of the upstream-third position of the 3' splicing site, and the sequence will skip exon or switch the 3' splicing site [6]. Even this small change in recognition characteristics is enough to greatly change the overall splitting situation and affect the splitting pattern of hundreds of genes. In particular, the mutation of U2AF1 has a "double-edged sword" effect on the differentiation of red blood cells, and the different positions of the mutation have different effects, which is an important hint of precision medicine [12].

3.3 SRSF2: Regulator of Exonic Enhancers

SRSF2 belongs to serine/arginine rich (Sr) protein group. Participate in the first splicing by finding the splicing enhancer of exon and helping U1 and U2 snRNPs gather at splice site. SRSF2 includes RNA recognition motif and RS domain. The former adheres to specific RNA sequences, while the latter acts as an intermediary between protein [6].

The multiplication of SRSF2 mostly occurs in proline 95 (P95H, P95L), an important part of RRM. Structural investigation shows that mutation of P95 can change the shape and electric distribution of the surface adhered to RNA, making it easier to find enhancer sequences with more G and more difficult to find sequences with more C [9]. This change of adhesion mode has widely changed the splicing of downstream target gene such as EZH2, CASP8 and BCAF1, and finally affected cell proliferation, apoptosis and epigenetic regulation. Mutation of SRSF2 can be found in 40%~50% of CMML, 25% of AML and 17% of MDS, all of which are related to poor prognosis [6][7].

4. DRUG DEVELOPMENT TARGETING SPLICING FACTORS

4.1 Structure-Guided Drug Discovery Paradigm

Drug discovery for SF3B1 is a successful example of the Structure guided approach. The steps are as follows: (1) Using cryo-EM to study the co-structure of the compound of target and lead, and reveal the correct combination way of natural product Pladienolide B and SF3B1 [13][14]; (2) Analyze the structure and clarify the mechanism of allosteric inhibition [15]; (3) Drawing the co-structure into a design drawing, and adopting molecular docking and computer aided drug design to improve the lead compound, so as to optimize its binding strength, sorting power, drug properties and in vivo activity.

Pladienolide B will stick in a deep waterproof pocket made of the HEAT repeating part of SF3B1. It's next to branch-point adenosine and U2 snRNA. This inhibitor works like a "wedge of molecules", preventing U2 snRNP from sticking firmly to pre-mRNA. Therefore, the assembly of spliceosome is not smooth, and a lot of uncut mRNA is accumulated [13][15]. This bonding method is the basis of all subsequent development of SF3B1 inhibitor.

4.2 Inhibitors Targeting SF3B1

4.2.1 Pladienolide B

Pladienolide B is a natural macrolide extracted from Streptomyces. As a splicing inhibitor, Pladienolide B was identified as the first compound targeting SF3B1 [13]. Although it has a strong function, it is difficult to carry out synthesis because of its low chemical stability, so it is difficult to carry out clinical development [16][17].

4.2.2 E7107

E7107 is the first clinical drug of Pladienolide B. Under the condition of keeping the central macrolide scaffold and key binding interactions unchanged, the pharmacokinetic properties are adjusted to be better [18]. E7107 is the first spliceosome inhibitor to enter clinical trials. In the study of Phase I, in some patients with progressive solid-tumor, it was found that the disease stopped developing or the tumor became smaller, and targeting SF3B1 had anti-tumor effect. However, the experiment was suspended because several patients developed severe and unpredictable optic neuropathy [18]. The mechanism of this toxicity is not completely clear, but it is thought that the susceptible cells like neuron will have an impact on important splicing events by stopping the action of wild-type SF3B1.

4.2.3 H3B-8800

H3B-8800 is a new generation of SF3B1 inhibitor. When making, more attention is paid to the efficacy of selecting SF3B1 with sudden variation and the benefits of absorption to the body when drinking it in the mouth ^[19]. According to the results of the structural investigation, the central part in the shape of a big circle was changed into a shape suitable for the pocket of SF3B1, and at the same time, a team was added to strengthen the special combination with the suddenly mutated protein.

The investigation on increasing the dosage of H3B-8800 (NCT02841540) Phase I was published in detail in 2025, indicating that the curative effect and possible risks of this experimental treatment are very important. The clinical trial is a low-risk myelodysplastic syndrome (MDS) which needs blood transfusion, and it is aimed at people with SF3B1 mutation. Participants were divided into two groups. Seven people in the first group drank 10mg twice a day, and 36 people in the second group drank 5mg twice a day. The most important effect criterion is that it doesn't matter if you don't transfuse red blood cells (RBC-TI) for more than 8 weeks. The survey results show that two people (28.6%) in the group with a large amount and two people (5.6%) in the group with a small amount have become the necessary RBC-TI for the minimum period. In terms of safety, it is reported as gastrointestinal problems, especially the most side effects of diarrhea. Due to the side effects, the dosage needs to be adjusted in 5 people (71.4%) of Cohort1 and 25 people (69.4%) of Cohort2. The most worrying thing is atrial fibrillation, which occurred in 2 (28.6%) and 7 (19.4%) patients in each cohort. The research team concluded that although the overall safety profile was consistent with the previous results, the cases of atrial fibrillation appeared to increase slightly. In addition, due to the low proportion of drug effect, it can be known that the used administration method has not achieved sufficient therapeutic effect, so additional research is needed to find a more effective administration method ^[25].

The clinical results of H3B-8800 show that in the previous clinical model, the selection of cancer cells that kill SF3B1 gene mutation ^[19] has the problem of insufficient effect and safety in actual clinical practice. This emphasizes the importance of adjusting the volume and selecting patients, so as to link the results of the laboratory with the treatment of patients.

4.3 Inhibitors Targeting U2AF1

All known U2AF1 inhibitors are still preclinical stage. U2AF1 is connected with U2AF2 through its own U2AF homology motif (UHM) domain and U2AF ligand motif (ULM) of U2AF2 to make a functional heterodimer. Based on this connection, researchers developed UHM domain inhibitors ^[12].

SF1-8 is a small molecule inhibitor aimed at the first U2AF1-UHM found in fragment-based screening. SF1-8 can select and inhibit the proliferation of leukemia cells and primary MDS cells with U2AF1 mutation by interfering with the combination of U2AF1 and U2AF2 ^[12]. AP232 is a derivative of SF1-8, and its inhibitory power on U2AF1 is increased by 3.1 times, which is 3 to 24 times more effective than other UHM protein selections. The study in 2025 further understood the anti-leukemic mechanism of AP232: AP232 changed the cell cycle process, reduced lysosomal acidification, blocked proliferation with G2/M and G1, interfered with autophagy and splicing factor mutant cells, and had stronger anti-leukemic effect ^[12].

In addition, a new precise gene-therapy method using synthetic introns is proposed. This is to select and destroy the cells of U2AF1-mutant MDS. This method makes use of the special splicing function of the mutated U2AF1. The establishment of synthetic introns can specifically identify the mutated splicing products and only kill the mutated cells ^[12]. This idea provides a brand-new approach for the treatment of U2AF1-mutant MDS.

4.4 Inhibitors Targeting SRSF2

For SRSF2-mutant hematologic cancers, currently developed inhibitors mainly rely on synthetic lethality and selective killing mechanisms.

ROCK inhibitors represent a highly promising preclinical class. SRSF2-mutant tumor cells are heavily dependent on ROCK-regulated microtubule-nuclear structure homeostasis; ROCK inhibition directly disrupts the microtubule network, induces nuclear deformation and mitotic catastrophe, thereby achieving selective killing of mutant cells ^[20]. RKI-1447, the most selective agent in this class, effectively suppresses proliferation of SRSF2-mutant AML cells in vitro and in xenograft models ^[20].

PRMT5 inhibitors is a clinical-stage drug which is aimed at SRS F2-Mutant Hematologic Malignancies, and has been studied most deeply at present. The important structure is this. The cancer cells of SRSF2-mutant become more dependent on PRMT5. PRMT5 inhibition will directly destroy the assembly of spliceosome, resulting in Synthetic Lethality ^[21].

Inhibitor's PRT543 is highly selective, suitable for patients with SRSF2-Mutant MDS/AML, and shows obvious effect in "Phase I studies" [21].

PARP inhibitors is another possible type, which uses the defects of DNA repair to work. SRSF2 mutations will lead to the abnormal increase of R-loops and weaken the DNA damage repair path. PARP inhibition further blocks the DNA repair of cancer cells, and makes mutant cells selectively produce apoptosis [22].

In addition, bortezomib of proteasome inhibitor is known to restore the sensitivity of SRSF2-mutant cells to inflammatory stimuli by increasing the amount of STAT1 protein, thus exerting therapeutic effects [23]. These different strategies reflect the complexity of SRSF2-mutant cancer. This is not only because it affects splicing, but also affects the abnormality of interferon signaling, the defect of DNA damage repair and other aspects [22][9].

4.5 Inhibitors Targeting Common Pathways: IRAK4 Inhibitors

Recent studies have shown that the mutations of splicing factor (including SF3B1, U2AF1, SRSF2) often lead to abnormal expression of long IRAK4-L isoform, which activates NF- κ B pathway, thus stimulating progenitor cells [24]. Since this discovery, the trend of developing IRAK4 inhibitors as a new treatment for mutant hematologic cancers has surged.

Emavusertib (CA-4948) is the only drug, and it is a small molecule of IRAK4 inhibitor through blood-brain-barrier. FLT3 and CLK/DYRK kinases also have inhibitory effects [24]. Their TakeAim Leukemia study (NCT04278768) is the most advanced clinical trial for splicing factor mutation.

Emavusertib (CA-4948) is a drug for stuttering. It is a small molecule IRAK4 inhibitor that can pass through blood-brain-barrier. FLT3 and CLK/DYRK kinases also have inhibitory effects [24]. In the TakeAim Leukemia study (NCT04278768), updated data as of 2025 showed that among 19 evaluable relapsed/refractory FLT3-mutant AML patients (with ≤ 2 prior lines of therapy) receiving the recommended Phase II dose (300 mg twice daily), 6 achieved complete remission (CR). Notably, most of these patients had received prior FLT3 inhibitors (e.g., midostaurin or gilteritinib), and many still responded to Emavusertib, suggesting potential to overcome resistance to prior FLT3 inhibitors. Clinical responses, including CR, were also observed in patients with splicing factor mutations, many of whom had been previously treated with hypomethylating agents plus venetoclax, indicating that Emavusertib may offer benefit even in heavily pretreated populations [24].

R289 is a prodrug of another dual IRAK1/4 inhibitor. In its Phase Ib study (NCT05308264), data presented at the 2025 ASH Annual Meeting showed that among 33 enrolled patients (median age 75 years, median prior lines of therapy 3), R289 was generally well tolerated. In the group using more than 500mg, among the patients who depend on blood transfusion, 33% (6/18) did not need red blood cell transfusion (RBC-TI) for more than 8 weeks [26]. Based on these data, R289 won the Orphan Drug Designation FDA in January 2025, and the Fast Track Designation in April 2026. The recommended dosage in Phase II will be decided later in 2026.

5. CLINICAL CHALLENGES AND FUTURE PERSPECTIVES

5.1 Balancing Efficacy and Safety

In the clinical development of spliceosome inhibitor, the most difficult thing is to strike a balance between efficacy and safety. E7107 stopped developing due to the occurrence of optic neuropathy [18]. H3B-8800 has been tried on many patients, but the effect is not ideal, and even atrial fibrillation has appeared [19]. This security problem may be because it hinders the wildtype splicing of normal cells, thus affecting the important splicing mechanism. When making the next generation of inhibitor, the important direction is to reduce the influence on wild-type spliceosome and make it only effective for mutant spliceosome [23].

5.2 Resistance Mechanisms

No matter what targeted therapies are, there is bound to be resistance. RUNX1 mutation is known to make SRSF2-mutant cells tolerate CHK1 inhibitors [9]. Alternative splicing themselves are also an important mechanism of cancer drug treatment. Tumors created transcriptomic plasticity and proteomic diversity by changing the way of splicing to cope with the power of therapy [1][2]. In the future research, we should seriously investigate the resistance mechanism of different types of splicing-factor mutation and work out the combination therapy that we are good at.

5.3 Expanding from Hematologic Cancers to Solid Tumors

The mutation of Splicing factor is not just hematologic malignancies. ^[6] is also often found in various solid tumor. In the future research, clinical trials will be conducted to apply the existing spliceosome inhibitor to these specific solid tumor species, and the situation of splicing required by each organization will be investigated. In addition, neoantigen produced by immune recognition splicing is the basis of precise TCR-T cell therapy for myeloid malignancies. Moreover, it is also worth studying to use immunomodulator and spliceosome inhibitor together ^[2].

5.4 New Technology-Driven Drug Discovery

The combination of generative artificial intelligence (ai) and structural dynamics opens a new way for drug discovery aiming at spliceosome. Using physical simulation and generative AI, researchers developed from static cryo-EM snapshots to dynamic structural engine research. Their goal is to reveal the state of immediate disappearance, find the hidden allosteric pocket, and aim at the inherently disordered region ^{[3][4]}. Through the change of this idea, we look forward to going beyond the limit of the current inhibitor design and finding a new spliceosome inhibitor.

6. CONCLUSION

The abnormality of Splicing factor is the main reason for the formation and deterioration of blood cancer. In addition, drugs targeting spliceosome will become a new treatment choice for these patients. From the discovery of Pladienolide B ^[13] to clinical trials of H3B-8800 ^[19] and Emavusertib ^[24], structural biology has fundamentally propelled the field from “undruggable” to “clinically accessible.” However, insufficient efficacy, safety concerns, and drug resistance remain major obstacles to widespread clinical application of spliceosome-targeted therapies. In the future, structure-based rational drug design, rational combination strategies, and deeper understanding of the functional heterogeneity of splicing factor mutations will collectively drive the field from “hematologic expansion” to “precision strike against solid tumors.”

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