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REVIEW ARTICLE

RNA-binding proteins as therapeutic targets in cancer

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ABSTRACT

RNA-binding proteins (RBPs) have emerged as critical regulators of cancer progression, influencing virtually all hallmarks of cancer. Their ability to modulate gene expression patterns that promote or inhibit tumorigenesis has positioned RBPs as promising targets for novel anti-cancer therapies. This mini-review summarizes the current state of RBP-targeted cancer treatments, focusing on five examples, eIF4F, FTO, SF3B1, RBM39 and nucleolin. We highlight the diversity of current targeting approaches and discuss ongoing challenges including the complexity of RBP regulatory networks, potential off-target effects and the need for more specific targeting methods. By assessing the future potential of novel therapeutic avenues, we provide insights into the evolving landscape of cancer treatment and the critical role RBPs may play in next-generation therapeutics.

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Introduction

RNA-binding proteins (RBPs) are crucial regulators of gene expression, orchestrating every phase of the mRNA lifecycle, from transcription and splicing to transport, stability and translation [1]. These versatile molecules dynamically interact with hundreds of RNA transcripts, both coding and non-coding, forming intricate regulatory networks that maintain cellular homoeostasis. RBPs bind to RNA forming ribonucleoprotein particles (RNPs). Recent research has revealed that the influence of these RNPs extends far beyond mRNA metabolism, including the assembly of membraneless compartments and the control of intracellular signalling [2–4]. The critical role RBPs play in cellular function underscores their significance in disease including, among others, neurodegenerative disease, autoimmune conditions, cardiovascular disease and cancer, pointing towards the targeting of RNA-protein complexes as a promising therapeutic avenue [5,6].

In recent years, significant efforts have been made to identify novel RBPs and generate a comprehensive map of these proteins [1,5,7]. Unbiased large-scale studies, such as RNA interactome capture (RIC), have dramatically expanded our knowledge of the RBP landscape [8,9]. To date, more than 4000 RBPs have been identified, highlighting the complexity and diversity of this protein family [5]. However, despite their abundance and critical functions, the exploration of RBPs as therapeutic targets remains in its infancy. This lag in development can be attributed to several factors that historically rendered RBPs 'undruggable'. One significant factor is that RBPs often lack the well-defined hydrophobic pockets typically found in enzymes, making traditional drug design less effective. Compounding this issue is the frequent presence of unstructured regions, further complicating drug design efforts [10]. Moreover, the high structural homology shared by several RBPs presents an important challenge in developing specific targeting strategies. Adding to these hurdles, the multifunctional nature of RBPs and their networking capacity makes it difficult to predict the downstream effects of RBP-directed therapies. RBPs interact with multiple RNA targets and other proteins within functionally related units known as 'RNA regulons' [11,12], complicating efforts to modulate one RBP without causing unintended side effects across the entire network. To address this challenge, researchers are developing sophisticated approaches that consider the context of RBP–RNA interactions. By taking into account both the secondary structure of the RNA and the nucleotides flanking the core-binding motif, which significantly influence RBP binding specificity, it is possible to design more accurate targeting strategies. Approaches that target particular transcripts rather than the RBP itself have been already successfully developed (see below). Alternatively, RBP or RNA modifications, required for certain RBP–RNA interactions can be exploited to further increase specificity.

Despite these difficulties, RBPs are emerging as promising targets and, as our understanding of RBP biology deepens and novel drug discovery approaches develop, first cases of successful RBP targeting have been described. A distinctive example of a life-saving drug inhibiting the binding of an RBP is Nusinersen (also called Spinraza), an antisense oligonucleotide (ASO) used to treat patients with spinal muscular atrophy (SMA) [13–15]. SMA is a motor neuron disease caused by an inactivating mutation in the Spinal Motor Neuron (SMN) 1 gene [16]. Lack of SMN protein leads to muscle weakness, respiratory distress and paralysis and patients generally succumb to the disease in the first 2 years of life [17,18]. A nearly identical gene, namely SMN2, produces only 10% of functional mRNA, as splicing leads to the exclusion of exon 7 from 90% of the mature SMN2 mRNA transcript.

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Nusinersen increases the production of SMN by masking an intronic splicing silencer in SMN2 pre-mRNA that would be otherwise recognized by hnRNP A1/A2, leading to exon 7 inclusion [14,19–22]. Nusinersen was approved in 2016 by the FDA [23] and represents a breakthrough in SMA treatment, offering hope to patients by addressing the underlying cause of the disease. Interestingly, small molecules promoting the inclusion of SMN2 exon 7 have now been identified and are in clinical trials [24–26]. The SMN example clearly demonstrates the potential of therapies targeting the interaction of RBPs with their binding sites on specific transcripts and paves the way to novel therapies for other genetic and multigenic pathologies including cancer.

The exploration of RBPs as potential therapeutic targets in cancer is an active and rapidly evolving field, and first promising candidates are already in clinical trials [27]. Various approaches to target RBPs or their interactions within RNP complexes are being considered, including small-molecule inhibitors (SMIs), ASOs, aptamers, peptides and more recently so-called molecular glues. Here, we examine examples of each of these categories to highlight their potential impact on cancer therapies. We focus on RBPs reaching the clinical trial stage, including eIF4F, FTO, SF3B1, nucleolin and RBM39. Apart from these, to the best of our knowledge only one other RBP, PRMT5, is currently under clinical trials for cancer treatment. However, drugs targeting PRMT5 do not interfere with RNA or protein interactions, but rather with its enzymatic methyltransferase activity, and hence are not further discussed here.

Targeting the translation initiation complex eIF4F – ASOs, SMIs

The eukaryotic initiation factor (eIF) 4F is a complex consisting of eIF4A, eIF4E and eIF4G, which plays a crucial role in translation initiation and is often dysregulated in cancer [28–30]. Among eIF4F complex components, eIF4E has emerged as a critical node of translational control, hyperactivated by several oncogenic pathways such as those controlled by Myc or Ras [31–34]. Importantly, reducing eIF4E levels specifically represses oncogenic transformation without affecting normal growth [35], highlighting the unique dependence of cancer cells on eIF4E and revealing a therapeutic opportunity.

eIF4E has indeed become a high-priority target for cancer treatment. Various strategies have been developed to inhibit eIF4E expression, post-translational modification, interaction with mRNA, or binding to protein partners (Figure 1, Nr. 1). One strategy involves downregulating eIF4E mRNA levels using DNA ASOs, which result in recognition of the DNA:RNA hybrid by RNase H followed by RNA degradation. Two different second-generation ASOs have been developed for this purpose, ISIS 183750 and LY2275796. ISIS 183750 was tested in a phase I/II clinical trial conducted in patients with advanced cancer (NCT01675128). This ASO was well-tolerated and eIF4E mRNA levels were downregulated in peripheral blood, but no objective tumour responses were observed, leading to the discontinuation of phase II trials [36]. Similarly, LY2275796 was well-tolerated but also failed to exhibit sufficient clinical efficacy in a phase I trial [37].

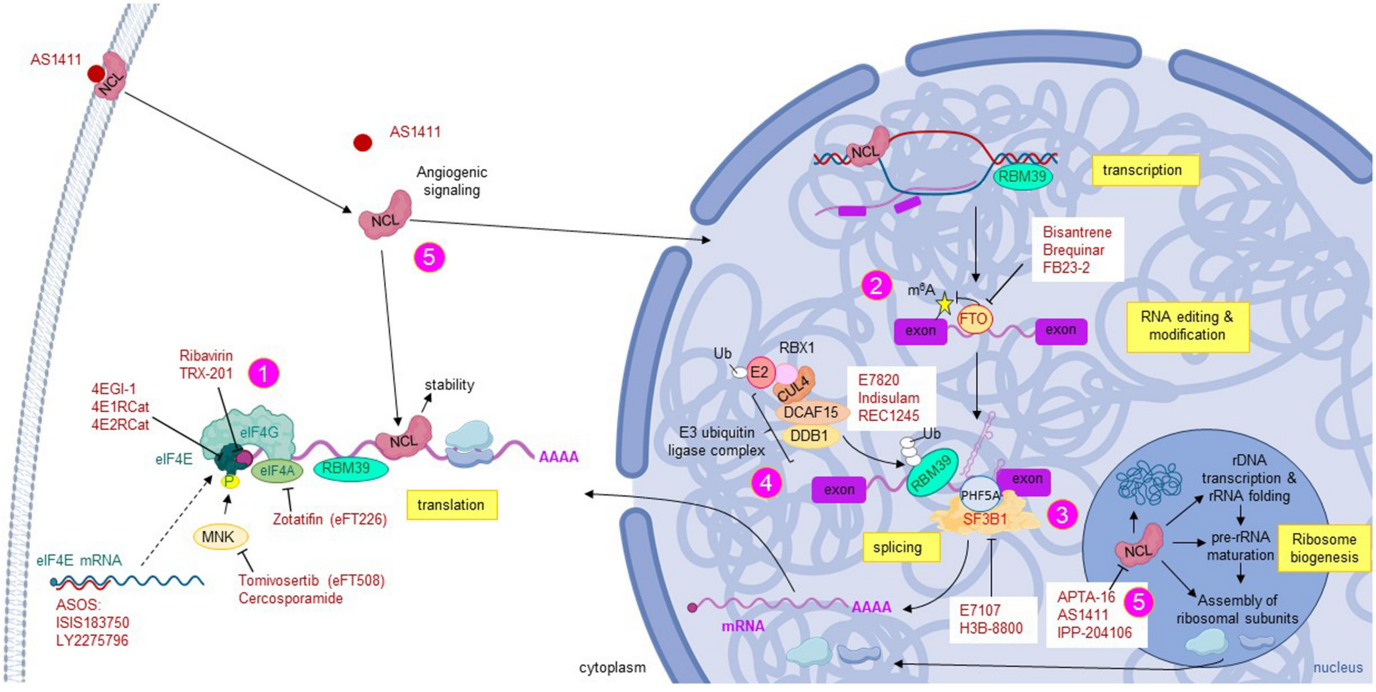

Figure 1. Therapeutic targeting of oncogenic RBPs. The figure illustrates the function of key RBPs (eIF4F, FTO, SF3B1, RBM39 and nucleolin) at various stages of the RNA life cycle (yellow boxes) and their respective inhibitors (red). Proteins are not drawn to scale. (1) eIF4F: Antisense oligonucleotides (ASOs) and small molecule inhibitors (SMIs) against different components of eIF4F reduce target mRNA translation. (2) FTO: SMIs bind to the catalytic pocket of FTO inhibiting RNA demethylation. (3) SF3B1: SMIs promote aberrant splicing, especially of transcripts containing weak branch points. (4) RBM39: Molecular glues promote the interaction of this factor with the E3 ubiquitin ligase complex, leading to its ubiquitination and subsequent degradation. (5) Nucleolin: aptamers and peptides inhibit this multifunctional protein, affecting several steps of gene expression.

Another strategy aims to inhibit the interaction between eIF4E and its site of binding on target mRNAs, the m^7G cap structure at the 5' end of transcripts. Ribavirin, an inhibitor of viral replication, and its derivative TRX-201, act as physical mimics of the m^7G cap. By binding to eIF4E, these compounds prevent its interaction with target mRNAs, reducing mRNA export and protein expression and leading to decreased cell proliferation and clonogenicity [38,39]. Ribavirin was tested in a phase II clinical trial as monotherapy for acute myeloid leukaemia (AML) showing initial clinical efficacy (NCT00559091) [38,40].

Blocking the interaction between eIF4E and eIF4G, which is critical for cap-dependent translation initiation and is often dysregulated in cancer [41,42], represents a third strategy. Small-molecule inhibitors such as 4EGI–1, 4E1RCat and 4E2RCat have demonstrated significant anti-tumour effects in preclinical models [43]. While 4EGI–1 disrupts the eIF4E–eIF4G interaction and promotes eIF4E binding to 4E-BP1, 4E1RCat and 4E2RCat block eIF4E association with both 4E-BP1 and eIF4G [44]. These compounds have shown efficacy in various cancer models and have the potential to reverse chemoresistance [43–46]. Additional compounds like ouabain and perillyl alcohol have also been identified as eIF4E-eIF4G inhibitors [47,48]. However, none of these compounds have reached clinical trials yet.

Phosphorylation of eIF4E by MAPK interacting serine/threonine kinases (MNKs) enhances its oncogenic activity [49,50]. Consequently, inhibiting eIF4E phosphorylation has emerged as another promising approach, representing one example of how specificity can be increased by targeting deployment of a modification, which in this case promotes translation of specific mRNAs [49,51]. MNK inhibitors like cercosporamide and tomivosertib (eFT508) have shown significant anti-cancer effects in preclinical studies [52–54]. Cercosporamide has exhibited potent antileukemic activity, particularly when combined with cytarabine or mTOR inhibitors, but no clinical trials with this compound have been registered [52]. Tomivosertib failed to provide sufficient benefit in a phase II clinical trial for non-small cell lung cancer (NCT04622007) and was discontinued.

Another component of the eIF4F complex, eIF4A, is also a valuable target for cancer therapy. eIF4A is an RNA helicase that unwinds structure in the 5' UTR allowing ribosome landing and initiation of translation [55]. Numerous eIF4A inhibitors have been developed and tested in preclinical and clinical studies. A comprehensive list of eIF4A inhibitors can be found in focused reviews [56]. One of these, Zotatifin (eFT226) was granted Fast Track designation by FDA in 2023 for combination therapies against metastatic breast cancer (NCT04092673). Zotatifin functions by stabilizing the binding of eIF4A to polypurine sequences in the highly structured 5'UTRs of mRNAs encoding oncogenes or pro-survival proteins, inhibiting their translation and leading to reduced proliferation [57]. Here, specificity is achieved by the increased dependence of these mRNAs on eIF4A.

In summary, translating promising preclinical results targeting eIF4F into clinical success remains a significant challenge – with inhibitors like Zotatifin showing potential – highlighting the need of further research into eIF4F-targeting strategies and a deeper understanding of cancer resistance mechanisms.

Targeting the m^6A demethylase FTO – SMIs

The RNA N^6-methyladenosine (m^6A) demethylase Fat mass and obesity-associated protein (FTO) functions as an oncogene in various cancers including AML, glioblastoma, breast cancer and pancreatic cancer, where it is aberrantly overexpressed [58,59]. It exerts its tumour promoting functions by regulating mRNA stability and translation through demethylation of m^6A and m^6Am [60,61]. Depletion of FTO effectively suppresses tumour progression, attenuates cancer cell metabolism and improves the response of cancer cells to therapeutic drugs [59,61]. On a molecular level, FTO knockdown or inhibition prevents cancer stem cell self-renewal and immune evasion [62], making FTO an outstanding promising target for cancer therapy. SMIs against FTO have been developed that block its catalytic pocket and disrupt its binding to m^6A-modified mRNA targets (Figure 1, Nr.2). One SMI called FB23–2, a derivative of meclofenamic acid, inhibits the progression of AML in xenograft models at high IC_{50} values [63]. Recently, however, two highly efficacious SMIs, bisantrene (CS1) and brequinar (CS2), with IC_{50} values in the low nanomolar range have been identified [62]. Bisantrene and brequinar interact with FTO residues key for interactions with mRNA targets (K216, S229, H231 and E234) [62]. They have demonstrated potent anti-tumour effects both *in vitro* and *in vivo* for the treatment of AML, and also minimal toxicity even at high doses. Bisantrene is currently in phase II clinical trials, raising hopes for potential treatment of elderly or chemotherapy-intolerant patients due to its low toxicity. Furthermore, as FTO inhibition can overcome immune evasion caused by hypomethylating agents, it is also a promising target for combination therapies.

Targeting the splicing factor SF3B1 - SMIs

The splicing factor 3B subunit 1 (SF3B1) is a crucial component of the spliceosome that recognizes the branch site and the helix formed by base pairing between U2 small nuclear (sn)RNA and the pre-mRNA, promoting the first step of the splicing reaction [64,65]. SF3B1 is one of the most frequently mutated splicing factors in human cancer [66]. Differences on splice site selection caused by SF3B1 mutation lead to more aggressive disease and shorter survival [67,68]. Natural compounds like spliceostatin A and pladienolide B, and its derivatives E7107 and H3B–8800 (RVT-2001), inhibit SF3B1 by binding to the interface of SF3B1 and PHF5A, another component of the U2 snRNP [69–71] (Figure 1, Nr.3). Although SF3B1 is essential for splicing of all introns, those with weak branch points are more sensitive to these compounds, including introns of genes related to cell division and apoptosis, potentially explaining their anti-cancer effects [72–78]. The case of SF3B1 illustrates how targeting a general and essential splicing factor yields effects on specific transcripts, making it a promising therapeutic target. Notably, E7107 and H3B–8800 have both progressed to phase I/II clinical trials; however, E7107 was discontinued due to severe side effects in some patients [79,80] and H3B–8800 was halted due to insufficient efficacy. This underscores the need for next-generation SF3B1 inhibitors with greater potency and improved safety profiles.

Targeting the splicing factor RBM39 – molecular glues

RNA Binding Motif Protein 39 (RBM39) is a multifunctional protein involved in the regulation of transcription, splicing and translation of tumour-related genes [81]. RBM39 is critical for the survival and progression of several cancer cell types, especially AML and malignant melanoma, and its overexpression is associated with breast cancer metastasis [82–84]. RBM39 has been considered undruggable because it lacks high affinity binding sites for conventional small molecule drugs. However, this changed after the emergence of molecular glues, a novel class of compounds that function by enhancing the affinity between two proteins [85]. Sulphonamides like indisulam (E7070) and E7820 facilitate the interaction of RBM39 with DCAF15 (DDB1 and CUL4-associated factor 15), a component of the E3 ubiquitin ligase complex, resulting in ubiquitination and degradation of RBM39 [81,86–88] (Figure 1, Nr. 4). E7820, indisulam, tasisulam and chloroquinoxaline sulphonamide all exhibit antitumor activity based on this principle [89–91]. The increased dependency of cancer cells on RBM39 and the frequent overexpression of DCAF15 in cancer cells, contribute to the increased activity of these drugs. Both indisulam and E7820 have been tested in multiple phase I and II clinical trials for solid tumours. While they demonstrate acceptable safety profiles, clinical efficacy has been so far modest and seems to be proportional to DCAF15 expression [86]. The newest molecular glue targeting RBM39, REC1245, has just cleared FDA approval for Phase I/II clinical trials in lymphoma and solid tumours enriched for DCAF15 (GDC30036410, GDCT0530892, planned start 12/2024).

Targeting the multifunctional protein nucleolin – aptamers, peptides

Nucleolin is a ubiquitous multifunctional protein mainly found in the nucleolus, but also present in the nucleoplasm, cytoplasm and plasma membrane. Apart from its main function in ribosome biogenesis, nucleolin plays an important role in chromatin organization, RNA metabolism and signalling [92–95] (Figure 1, Nr. 5). Nucleolin is overexpressed on the surface of cancer cells in many tumours, including non-small cell lung cancer, neuroblastoma, gastric, ovarian, breast and kidney cancer, where it serves as a receptor for ligands implicated in angiogenesis, proliferation, cell survival and metastasis [96–100]. Given its selective presence on the plasma membrane of cancer cells and its multifaceted influence on tumour progression, nucleolin is a remarkable target for cancer therapy with promising specificity. This has been confirmed by the anti-angiogenic and anti-proliferative properties of nucleolin antagonists [101,102]. The complexity of nucleolin structure made it suitable for the development of aptamers, short single stranded nucleic acids designed to bind to their targets with high affinity [103]. To date, only five therapeutic aptamers have made it to clinical trials for the treatment of cancer, two of them (AS1411 and APTA-16) targeting nucleolin [104–106]. AS1411 is a 26-nucleotide DNA-based aptamer forming a stable G-quadruplex structure. Upon binding, the AS1411:nucleolin complex is internalized, resulting in decreased binding of nucleolin to the mRNA encoding the anti-apoptotic factor Bcl-2, and leading to Bcl-2 mRNA destabilization and induction of apoptosis (Figure 1, Nr.5) [107]. Additionally, AS1411 downregulates the N-terminal phosphorylation of nucleolin, leading to the inhibition of rRNA transcription [108]. AS1411 has been tested in several phase II clinical trials for patients with refractory metastatic renal cell carcinoma and relapsed AML (NCT00740441; NCT00512083). In general, AS1411 was well tolerated but showed limited efficacy in unselected patients as monotherapy. However, in combination with the anti-cancer drug cytarabine, an improved response in AML patients was observed [109]. Remarkably, AS1411 has been used in drug delivery platforms to increase specific targeting of cancer cells [110]. For example, this aptamer has been used to enhance the specificity of gene therapy approaches, by conjugating it to the capsid protein of adeno-associated viruses in order to increase their selective uptake by cancer cells [111]. APTA-16 is a truncated version of AS1411 consisting of only 16 DNA-bases that is being used as an aptamer–drug conjugate in phase I/II clinical trials for patients with refractory AML (https://aptabio.com/science/science03.php). Noteworthy, complementary approaches based on inhibiting nucleolin with synthetic peptides are also ongoing (Figure 1, Nr.5). For example, the pseudopeptide IPP-204106 (N6L) is currently in phase II clinical trials for patients with pancreatic, bladder, lung and metastatic breast cancer [112,113] (NCT01711398).

Conclusions and future perspectives

RBPs have been long considered undruggable, but recently this dogma has changed, positioning RBPs as promising novel targets for cancer therapy. This is reflected in the diversity of approaches being explored to target RBPs including SMIs, ASOs, aptamers, synthetic peptides and molecular glues. One important consideration, however, is that many RBPs are not only essential for cancer cell survival but also for normal cell growth. Hence, it is essential to understand the specificity determinants that distinguish the function of RBPs in benign versus malignant contexts, such as specific RBP–RNA or RBP–protein interactions, or tumour-related post-translational modifications, which could be targeted to limit therapy toxicity. To maximize effectiveness, targeted delivery systems through recognition of cancer-specific cell surface markers, highlighted here with the example of nucleolin, could be essential. The field is rapidly evolving, and nanoparticles recognizing such markers to deliver ASOs, SMIs and other drugs are at the forefront of current research [114–116].

Targeting RBPs represents an opportunity in cancer treatment strategies. First, the diverse roles that RBPs play across different cancer types and stages offer exciting possibilities for developing personalized therapeutic approaches. Second, RBP-targeted therapies could synergize with existing treatments, such as chemotherapy or immunotherapy, to enhance their efficacy and potentially overcome resistance mechanisms. Certain RBPs have been implicated in pathways that contribute to immunotherapy resistance either by remodelling tumour cells to evade immune responses or by directly modulating such responses. For instance, eIF4E

promotes tumour immune evasion by upregulating the expression of PD-L1, a target of immune checkpoint inhibitors [117]. The RBP ADAR1, on the other hand, regulates immune function [118] and plays a role in immune resistance by regulating ICAM1 expression [119]. Thus, targeting these RBPs could improve immunotherapy approaches.

To fully harness the immense potential of RBP targeting therapies, however, substantial research is required. Most basic research studies are carried out on immortalized or cancerous cells, and the function of many RBPs in normal physiology remains obscure. Critical differences in RBP function between normal and cancerous tissues need to be identified, exploiting state-of-the-art experimental systems such as organoids, organ-on-chip or tissue explants. A deeper understanding of RBP biology, including nuanced comprehension of their molecular interactions, structural diversity and context-specific functions, combined with novel approaches in drug discovery and delivery, will provide a robust foundation for developing transformative and effective cancer therapies based on RBP targeting.

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Author contributions

JJ wrote the first version of the manuscript and FG edited it. All authors have read and approved the final work.

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