Multifaceted regulatory role of proline- and glutamine-rich splicing factor in tumors (Review)

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Abstract. Proline- and glutamine-rich splicing factor (SFPQ) is an RNA-binding protein that is predominantly localized in the nucleus and plays a multifaceted regulatory role in the process of gene expression. The functions of SFPQ include the promotion or inhibition of gene transcription, pre-mRNA splicing, mRNA processing, transport and localization, and translation. The primary impact of SFPQ on cellular processes is the regulation of cell cycle progression and apoptosis. In addition, SFPQ represents an important element of paraspeckles, exerting a notable influence on gene expression within the nucleus. The expression of SFPQ is altered in tumors, promoting the development and drug resistance of tumors in various ways, notably altering the prognosis of patients. In the present review, the fundamental physiological functions of SFPQ and its particular effects on tumorigenesis and development are discussed.

Contents

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1. Introduction

Proline- and glutamine-rich splicing factor (SFPQ), also known as polypyrimidine tract-binding protein (PTBP)-associated splicing factor, was identified in 1993 during the characterization of a complex of PTBPs that was hypothesized to be important for early precursor mRNA splicing (1). SFPQ was subsequently named based on its abundance of proline and glutamine. SFPQ is an RNA-binding protein (RBP) and along with the nuclear proteins non-POU domain-containing octamer-binding protein (NONO), paraspeckle component 1 (PSPC1), it belongs to the conserved drosophila behavioral human splicing (DBHS) family of proteins (2). Studies have shown that the three proteins of this family are commonly found to be colocalized and function in a variety of contexts by forming heterodimers. SFPQ is primarily localized to paraspeckles (3), nuclear speckles (4), the nucleoplasm (5) and the nucleolus cap (6) within the nucleus. It possesses RNA-, protein- and DNA-binding domains, which enable it to extensively regulate the entire process of gene expression. This encompasses transcriptional activation or repression, pre-mRNA splicing, mRNA modification and internal ribosome entry site (IRES)-mediated translation, among other functions (7-17). Furthermore, SFPQ plays a role in DNA damage repair and affects apoptosis (18-26). A growing body of evidence indicates that it exerts a marked influence on cellular activity. Given its extensive range of actions, SFPQ plays a notable role in regulating the normal physiological functions of a multitude of cell types within living organisms. Its dysregulation has been linked to the onset and progression of a spectrum of diseases, including neurodegenerative disorders and spinal muscular atrophy (27,28). The protein was first discovered 30 years ago, and in recent years, there has been an increase in studies indicating that the dysregulation of SFPQ is linked to tumor development (29-33). However, due to the wide range of targets and the complexity of its role, the study of the function of SFPQ in tumors remains in the preliminary stage of exploration. The present review primarily focuses on the various specific molecules that SFPQ binds to and regulates, as well as its role in different cancers.

The full-length protein of SFPQ is comprised of 707 amino acids, and at least seven structural domains have been delineated thus far through the analysis of amino acid sequences and

functions (Fig. 1) (34). From the N-terminus, these are the RGG box, the proline-rich domain, the two RNA recognition motifs (RRMs), the NONA/paraspeckle (NOPS) structural domain, the coiled-coil domain, the C-terminal domain (CTD) and a Proline-RRM-linked domain that connects the proline-rich domains to the RRMs. The RGG box is a 27-amino acid sequence located at the N-terminal end of SFPQ. It comprises multiple trimeric RGG repeats and has been demonstrated to confer RNA-binding activity. Additionally, proteins containing RGG domains have been shown to mediate interactions with DNA and proteins (34-38).

The RRM is widely found in a variety of RBPs. The two RRMs contained in SFPQ play an important role in its normal functioning. In addition to directly mediating RNA binding, RRMs also mediate SFPQ interactions with other proteins (39,40) and the subnuclear localization of SFPQ (4). The deletion of RRM2 results in the diffuse accumulation and loss of nuclear speckle localization. The NOPS domain is indispensable for the formation of paraspeckles. Point mutations in this domain result in SFPQ losing its ability to localize to paraspeckles (41). Paraspeckles are membrane-less subnuclear bodies within the nucleus, composed of the long non-coding RNA (lncRNA) nucleus-enriched abundant transcript 1 (NEAT1) serving as a molecular scaffold, which assembles with RBPs, including SFPQ and NONO. They function by retaining specific mRNAs to modulate gene expression and play important roles in cellular stress responses (42). The coiled-coil domain enables SFPQ to form dimers with other DBHS family proteins, thereby facilitating the formation of paraspeckles (41). The domains of SFPQ indicate that SFPQ is predominantly localized in the nucleus, where it performs a series of functions by forming heterodimers with other DHBS proteins to form paraspeckles.

2. SFPQ widely regulates gene expression

Regulation of epigenetics and gene transcription. In normal cells, SFPQ exerts inhibitory or activating effects on gene transcription by binding to various proteins, including RNA polymerase II (9,10), histone deacetylase (HDAC) (12,14,15,43) and lysine-specific histone demethylase 1 (LSD1) (44). It has been demonstrated that the binding of full-length SFPQ to the DNA-binding structural domain of nuclear hormone receptors notably enhances the repressive effect of the nuclear hormone receptor thyroid hormone receptors (TRs) and retinoid X receptors on target genes in the absence of the hormone ligand. Furthermore, it was determined that SFPQ binds to amino acids 404-545 of paired amphipathic helix protein Sin3a (SIN3A), which in turn recruits the SIN3A/HDAC complex to mediate the transcriptional repression of the nuclear hormone receptor (Fig. 2). This effect can be reversed by the HDAC inhibitor sodium butyrate. Finally, the aforementioned study found that SFPQ and SIN3A do not dissociate from TR/retinoic acid receptor complex *in vivo* in the presence of its ligand, suggesting that the intracellular distribution and content of SFPQ may play a fine-tuning role in this transcriptional repression (12).

In renal cell carcinoma (RCC), the transcriptional repressor complex formed by SFPQ/transcription factor E2F1/HDAC1 has been demonstrated to mediate transcriptional repression of multidrug and toxin extrusion protein 2 (MATE 2-K). MATE 2-K is encoded by the gene solute carrier family 47 member 2 (*SLC47A2*), which plays a role in the secretion of certain endogenous and exogenous compounds. Low expression of *SLC47A2* is associated with a poorer prognosis in RCC (45). In 2016, it was indicated that SFPQ binds to LSD1 and regulates the migration of nascent pyramidal neurons in the developing cerebral cortex (44). LSD1, also known as KDM1A, is a histone demethylase that functions as a transcriptional activator or repressor of specific genes by forming complexes with various proteins and catalyzing the demethylation of histone 3 lysine residue 4 (H3K4) or H3K9 (46). In the context of cortical development, the knockdown of LSD1 has been shown to result in a transient delay in the migration of newborn pyramidal neurons, accompanied by an increase in the number of progenitor cells. The study validated the direct physical interaction of SFPQ with LSD1 and discovered that neurons exhibit a progressive increase in SFPQ expression as they migrate and differentiate (47). Furthermore, SFPQ depletion results in marked abnormalities in cell migration within the brain and alters the proliferative behavior of progenitor cells in the developing cerebral cortex (44). In tumor cells, LSD1 functions to either promote or repress the transcription of metastasis-associated genes through epigenetic regulation, thereby facilitating the epithelial-mesenchymal transition process in a variety of tumors, including breast cancer (48). Despite the lack of research elucidating the direct interaction between SFPQ and LSD1 in tumors and the impact of this interaction on the tumor genome, the present review can serve as a valuable reference for studies examining the regulation of LSD1 and SFPQ in tumors.

Furthermore, SFPQ has been suggested to have the capacity to bind DNA directly, thereby exerting transcriptional repression (49). Insulin-like growth factor (IGF)-I functions as a transcription factor, regulating the expression of genes containing IGF response elements (IGFREs). SFPQ can bind to the 5' end of the IGFRE GC box, thereby inhibiting IGF-I-mediated gene transcription (50). In hypoxic conditions, the expression of the lncRNA LHFPL tetraspan subfamily member 3-antisense RNA 2 (LHFPL3-AS2) is decreased in non-small cell lung cancer (NSCLC). This results in a reduction in the binding of LHFPL3-AS2 to SFPQ, leading to the release of free SFPQ and its binding to the promoter of the gene *thioredoxin-interacting protein* (*TXNIP*), which inhibits its expression. *TXNIP* is a tumor suppressor gene that can inhibit the expression of metastasis-associated genes through the TGF-β signaling pathway. Consequently, the expression of *TXNIP* is repressed when the concentration of free SFPQ is elevated, thereby facilitating tumor migration and invasion (Fig. 3) (51).

SFPQ has also been demonstrated to bind to the *IL8* promoter, thereby repressing its transcription. Furthermore, NEAT1 splicing variant 2 (NEAT1v2) expression has been observed to increase during viral infection, which in turn induces an increase in paraspeckle formation. The increase of NEAT1 expression induces the relocation of SFPQ from the *IL8* promoter to the paraspeckle, thereby promoting the expression of antiviral genes, such as *IL8*, C-X-C motif chemokine ligand 8 (*CXCL8*), antiviral innate immune response receptor *RIG-I* and DEAD box protein 60 (16,52). Additionally, the

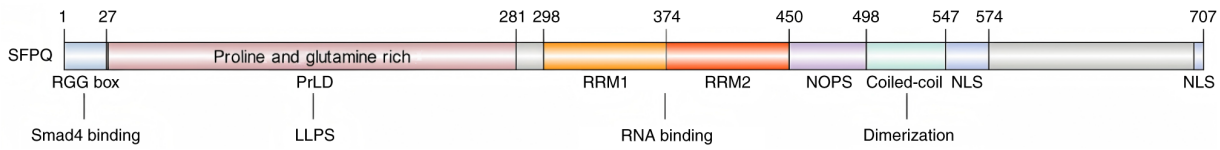

Figure 1. Domain structure of SFPQ. The schematic illustrates key functional domains within the SFPQ protein. Each domain is identified by its name and the range of amino acid residues it encompasses (numbers indicated above each domain boundary). The depicted domains are important for protein and RNA binding, dimerization and phase separation. PrLD, prion-like domain; LLPS, liquid-liquid phase separation; RRM, RNA recognition motif; NOPS, NONA/paraspeckle structural domain; NLS, nuclear localization sequence; SFPQ, proline- and glutamine rich splicing factor.

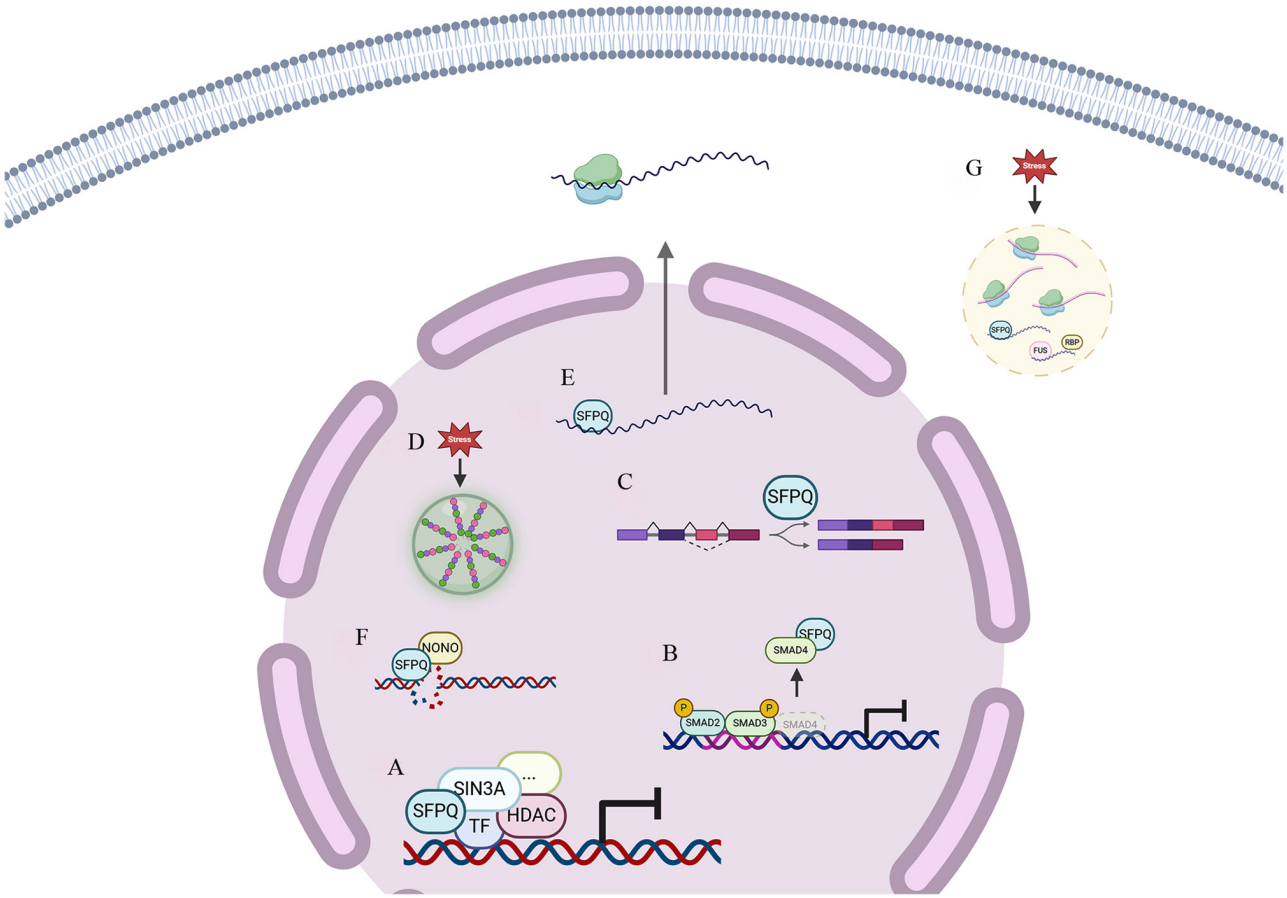

Figure 2. Mechanism of SFPQ regulating gene expression. A, SFPQ recruits epigenetic regulators, such as SIN3A and HDAC, and represses gene expression. B, SFPQ undergoes liquid-liquid phase separation with some transcriptional factors, such as Smad4, thereby inhibiting gene expression mediated by the Smad complex. C, SFPQ regulates alternative splicing. D, SFPQ is an important component of paraspeckles, which responds to stress conditions by RNA editing and RNA nuclear retention. E, SFPQ mediates mRNA editing and subcellular localization. F, SFPQ takes part in DNA repair. G, SFPQ is also a component of stress granule. Created in https://BioRender.com. SFPQ, proline- and glutamine-rich splicing factor; HDAC, histone deacetylase; SIN3A, paired amphipathic helix protein Sin3a; TF, transcriptional factor; P, phosphate group; NONO, non-POU domain-containing octamer-binding protein; FUS, RNA-binding protein FUS; RBP, RNA binding protein.

N6-methyladenosine (m6A) demethylase alkylated DNA repair protein alkB homolog 5 (ALKBH5) is upregulated in glioblastoma multiforme (GBM) under hypoxic conditions, resulting in the erasure of m6A deposition in the lncRNA NEAT1. This process stabilizes the transcript and facilitates NEAT1-mediated paraspeckle assembly, which similarly leads to the relocation of SFPQ from the *CXCL8* promoter to the paraspeckle and ultimately upregulates CXCL8/IL8 expression (53).

SFPQ promotes precursor mRNA splicing, RNA processing and localization. SFPQ was initially identified in splicing-associated complexes with important roles in early precursor mRNA splicing (2). Subsequent studies have elucidated the functions played by SFPQ in spliceosomal complexes. In the nucleus of eukaryotic cells, upon transcriptional activation, RNA polymerase II is enriched at the promoters of genes to catalyze transcriptional elongation. Meanwhile, the CTD of RNA polymerase II influences the removal of the first intron by interacting with SFPQ, facilitating the efficient processing of precursor mRNAs and coordinating transcription and mRNA processing (54). Furthermore, the death-inducer obliterator 3 amino-terminal of RNA polymerase II has been observed to bind to histone and polymerase mandibular structural

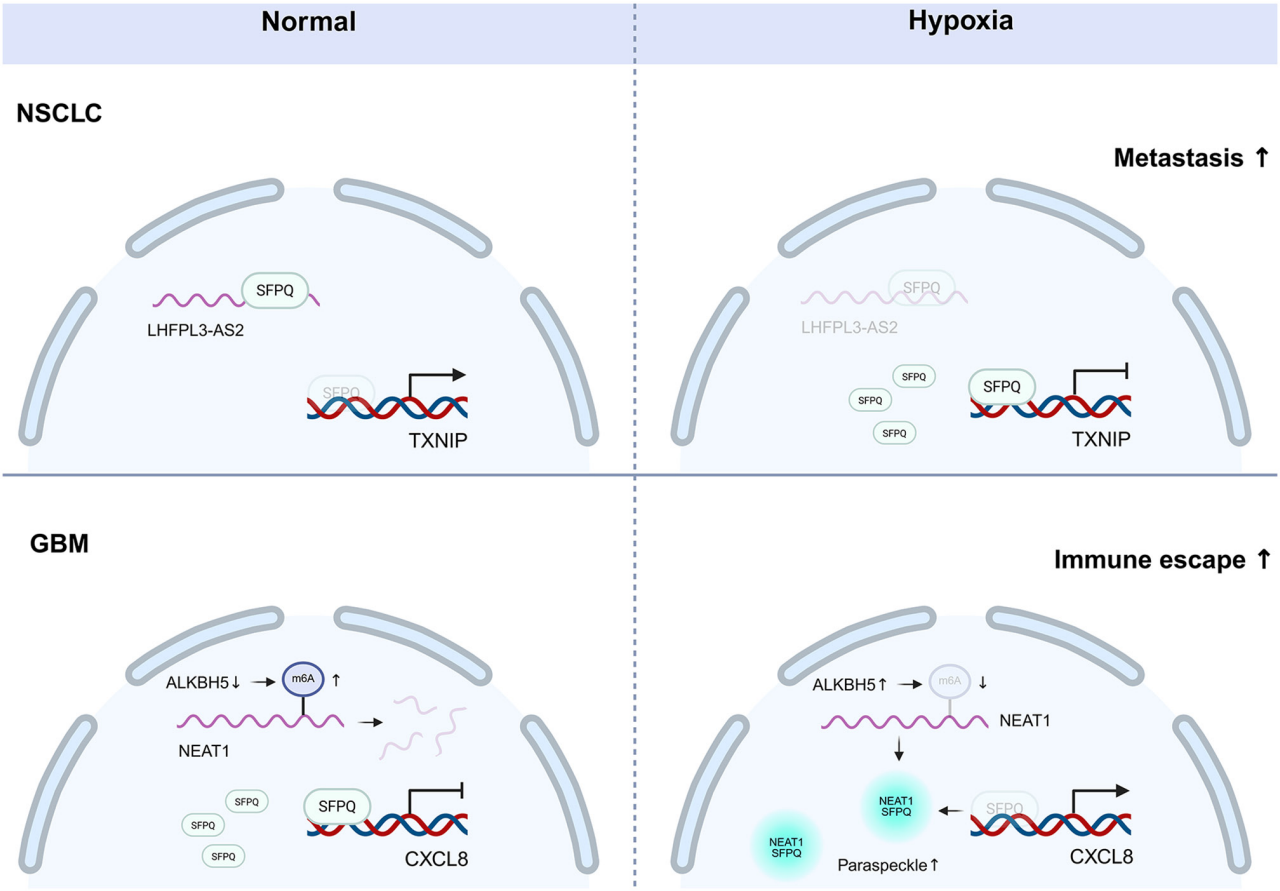

Figure 3. A schematic representation of SFPQ regulating transcription in cancer. The schematic depicts the differential regulatory effects of SFPQ on gene expression in NSCLC (top panels) and GBM (bottom panels) under normoxic and hypoxic conditions. Created in https://BioRender.com. NSCLC, non-small cell lung cancer; GBM, glioblastoma; LHFPL3-AS2, LHFPL tetraspan subfamily member 3-antisense RNA 2; TXNIP, thioredoxin-interacting protein; ALKBH5, alkylated DNA repair protein alkB homolog 5; NEAT1, nucleus-enriched abundant transcript 1; CXCL8, C-X-C motif chemokine ligand 8; SFPQ, proline- and glutamine-rich splicing factor; m6A, N6-methyladenosine.

domains, while its carboxy-terminus has been shown to recruit SFPQ and facilitate the selective splicing of mRNAs. A mutation in dido has been demonstrated to impede the binding of SFPQ to RNAs and precipitate a considerable increase in the number of exon skips (55).

It has been demonstrated that cells are able to regulate intracellular protein reserves through variable splicing in response to stimulation of external signals. Numerous studies have reported the effects of SFPQ on the variable splicing of different proteins. For instance, SFPQ has been shown to mediate exon skipping of CD45 in order to regulate T-cell homeostasis and activation (23). Under cellular senescence, the autophagy receptor next to BRCA1 gene 1 protein selectively degrades SFPQ, leading to enhanced skipping of exon 5 in the eukaryotic translation initiation factor 4H (EIF4H) pre-mRNA. This splicing alteration drives proteome remodeling associated with the senescence-associated inflammatory phenotype. Furthermore, EIF4H alternative splicing has been linked to clinical prognosis across multiple cancer types (56). Additionally, SFPQ has been observed to bind with enhancer sequences on survival motor neuron protein (*SMN*)*2* exon 7, which promotes splicing and results in the rapid degradation of SMNΔ7 (27). In tumor cells, SFPQ also affects processes such as antitumor immunity and metastasis through selective splicing. For instance, in hepatocellular carcinoma (HCC), there is an increase in NONO expression, which is accompanied by an interaction with SFPQ that promotes the inclusion of exon 12a of Myc box-dependent interacting protein 1. This exon inclusion exerts oncogenic activity (Fig. 4A) (57). In models including colorectal cancer, melanoma and lymphoma, TGF-β has been shown to upregulate SFPQ, which subsequently binds to Irf1 pre-mRNA to promote its alternative splicing into the Irf1Δ7 isoform, thereby attenuating Th1 cell activity (58). NONO interacts with SFPQ to regulate exon jumping of SET domain and mariner transposase fusion gene (SETMAR); the SETMAR-long isoform can inhibit the transcription of metastasis-associated genes by inducing trimethylated histone H3 at lysine 27 (H3K27me3) on their promoters, thus inhibiting lymphatic metastasis of bladder cancer cells (Fig. 4B) (59).

As a prevalent modification of mRNAs, m6A methylation occurs immediately after transcription of mRNA precursors in the presence of methyltransferase-like 3. Conversely, fat mass and obesity-associated protein (FTO) and ALKBH5 are responsible for m6A demethylation. It has been demonstrated that alterations in m6A modification patterns are linked to tumorigenesis, including breast cancer, lung cancer, acute myeloid leukemia and GBM (60). The m6A modification may regulate mRNA splicing by interfering with the interaction between splicing factors and mRNAs, affecting the nuclear

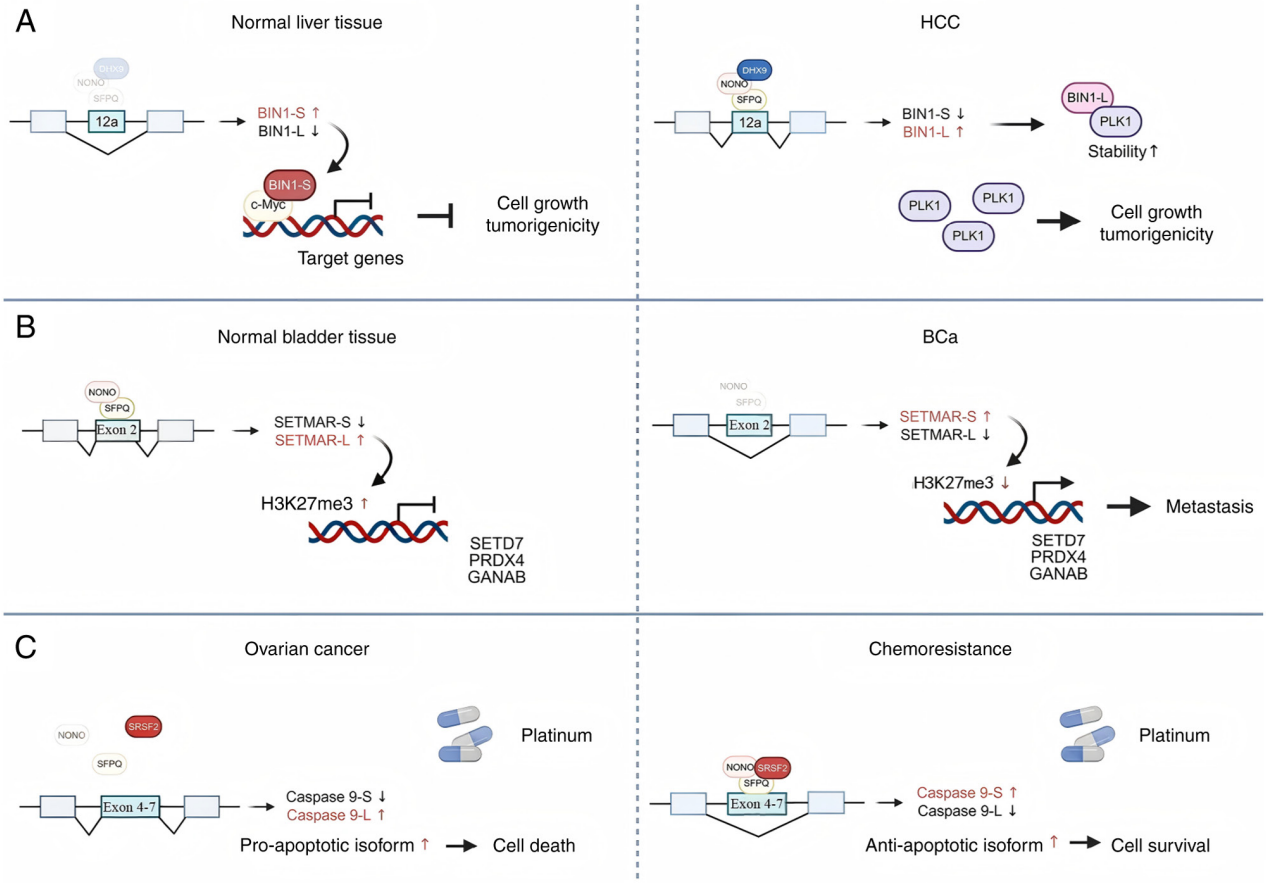

Figure 4. A schematic representation of SFPQ regulating alternative splicing in cancer. (A) In normal liver tissue, the long isoform of BIN1 is expressed at high levels and suppresses c-Myc-induced downstream gene expression. In HCC, upregulated SFPQ promotes exon 12a inclusion in BIN1 pre-mRNA, shifting the BIN1 isoform balance towards the long isoform. This increased abundance of the long BIN1 isoform stabilizes PLK1, thereby promoting tumorigenesis. (B) In BCa, downregulation of SFPQ promotes skipping of the second exon of SETMAR, increasing the proportion of the short SETMAR isoform. This isoform shift reduces H3K27me^3 levels, leading to enhanced expression of pro-metastatic genes and promoting metastasis. (C) In platinum-resistant ovarian cancer cells, upregulated SFPQ mediates the skipping of exons 4-7 in caspase-9 pre-mRNA. This promotes accumulation of the anti-apoptotic long isoform of caspase-9, resulting in enhanced cell survival. Created in https://BioRender.com. HCC, hepatocellular carcinoma; BCa, bladder cancer; BIN1, bridging integrator 1; BIN1-S, BIN1 short isoform; BIN1-L, BIN1 long isoform; NONO, non-POU domain-containing octamer binding; SETMAR, SET domain and mariner transposase fusion gene; SETMAR-S, SETMAR short isoform; SETMAR-L, SETMAR long isoform; SETD7, SET domain containing 7; PRDX4, peroxiredoxin 4; GANAB, glucosidase II α subunit; SRSF2, serine and arginine rich splicing factor 2; SFPQ, proline- and glutamine-rich splicing factor; DHX9, ATP-dependent RNA helicase A; 12a, exon 12a of c-Myc; PLK1, serine/threonine-protein kinase PLK1; caspase 9-S, caspase 9 short isoform; caspase 9-L, caspase 9 long isoform; H3K27me^3, histone 3 lysine residue 27 trimethylation.

export of mRNAs, regulating mRNA translation and influencing mRNA stability (61). In 2020, it was demonstrated that SFPQ is an FTO-binding protein that regulates substrate selection by FTO. The binding motif for SFPQ is CUGUG, which enables SFPQ to recruit FTO and facilitate demethylation at sites in close proximity to this motif. The data indicate that FTO exhibits a preference for binding to CUGUG sites in the presence of SFPQ compared with CUGUG sites in the absence of SFPQ. This suggests that the selectivity of FTO for RNA is less related to the CUGUG motif and more closely related to SFPQ. In HeLa cells, the methylation of MYC and NEAT1v2 mRNA was markedly reduced following SFPQ overexpression. These findings suggest that in tumor cells, SFPQ may affect mRNA splicing, localization and translation of oncogenes by determining the substrates of FTO (62).

In addition to regulating alternative splicing and modification of mRNAs, SFPQ modulates microRNA (miRNA)-mediated post-transcriptional gene silencing by influencing both miRNA biogenesis and activity (63). A study demonstrated that SFPQ, as a constituent of the miRNA-containing RNA induced silencing complex, specifically binds to the 3'untranslated region (UTR) regions of select mRNAs and modulates their folding. This structural regulation enhances the silencing efficacy of specific miRNAs on these target mRNAs while preventing stochastic nonproductive miRNA interactions (64).

Furthermore, SFPQ plays a role in the subcellular transport of RNA. In neurons, SFPQ binds to kinesin family member 5A and kinesin light chain 1, which is responsible for translocating mRNAs to axon terminals for localized protein synthesis (65). Additionally, SFPQ has been shown to mediate the export of estrogen receptor (ER) mRNAs from the nucleus, thereby facilitating their translation in breast cancer (66).

SFPQ affects IRES-mediated regulation of translation. SFPQ plays a role in translation via the cytoplasmic IRES, a complex secondary or tertiary RNA structure within mRNA that facilitates ribosome assembly. SFPQ has been demonstrated

to bind directly to IRES elements within p53 (8). Furthermore, during TNF-related apoptosis-inducing ligand-induced apoptosis, SFPQ has been shown to regulate IRES-mediated translation of a range of apoptosis-related genes (24). It is well documented that mutations in the Ras protein are a common occurrence in a number of different types of human cancer, including pancreatic cancer, lung adenocarcinoma and colorectal carcinoma (CRC). The activation of RAS mutations has been observed to result in the promotion of tumor progression, with the regulation of gene expression networks being a key factor in this process (67). It was observed that upon activation of the Ras pathway, casein kinase 1α (CK1α) phosphorylates FOXO4 and promotes its proteasomal degradation, thereby inhibiting FOXO4-mediated tumor suppression (68). In this process, SFPQ can bind to the 5'UTR of CK1α mRNA, thereby promoting IRES-mediated translation of CK1α (29).

3. SFPQ affects tumorigenesis and progression

SFPQ has a regulatory role in tumorigenesis. The loss of TGF-β-mediated cell growth inhibition at the early stages of tumorigenesis represents one of the hallmarks of cancer. This is characterized by the suppression of target genes that are regulated by the Smad complex, which in turn promotes tumor cell proliferation. Inhibition of the TGF-β pathway in some tumors is caused by inactivating mutations or deletions of TGF-β signaling components such as Smad4. However, such mutations are less common in certain tumor types, indicating that there are alternative mechanisms that lead to the inhibition of the TGF-β signaling pathway (69).

It has been demonstrated that the overall survival rate of patients with HCC and high expression of SFPQ is markedly inferior to that of patients with HCC and low SFPQ expression. Furthermore, the protein level of SFPQ has been shown to be positively associated with the tumor size of patients with HCC, and recurrence is frequently observed in patients with HCC and high SFPQ expression. The lowest expression of SFPQ is observed in stage I tumors, while the highest expression is seen in stage III and IV tumors (32). The knockdown of SFPQ was shown to inhibit the proliferation, migration and invasion of HCC cells (32,33). Further analysis revealed that SFPQ in HCC drives liquid-liquid phase separation (LLPS) through its prion-like structural domain and binds to Smad4 through the structural domain of the RGG box. The initial 27 amino acids at the N-terminal end of the RGG box, referred to as the Smad-binding domain, results in the formation of a droplet with Smad4, which physically obstructs the formation of complexes between Smad4 and Smad2, as well as Smad3, thereby triggering the dissociation of Smad complexes. The deletion of SFPQ results in the upregulation of Smad downstream target genes, including plasminogen activator inhibitor 1 and cyclin-dependent kinase 4 inhibitor B, while the expression of MYC is downregulated. This positively affects DNA synthesis and the cell cycle, leading to the inhibition of tumor cell proliferation (33). Nevertheless, it should be noted that TGF-β exerts a dual regulatory role in tumors, and that the aforementioned study only explored the role of SFPQ/LLPS in the TGF-β growth inhibitory signaling pathway and in the initiation stage of HCC, without further investigation into the progression and metastasis. A further study demonstrated that upon oncogenic activation in HCC, mTOR complex 1 suppresses NEAT1v2 expression and parafollicular biogenesis, resulting in the release of NONO/SFPQ. Subsequently, NONO/SFPQ binds to U5 in the spliceosome, stimulating mRNA splicing and the expression of key glycolytic enzymes, thereby enhancing glucose transport, aerobic glycolytic flux, lactate production and HCC proliferation and growth *in vitro* and *in vivo* (70).

Furthermore, a study of CRISPR genome-wide knockdown analysis of melanoma cells revealed that these cells exhibited a high degree of dependency on SFPQ. This was evidenced by the notable upregulation of SFPQ observed in tumor cells relative to normal tissues. Additionally, knockdown of SFPQ was found to impede proliferation, migration and glycolysis, as well as promote apoptosis in tumor cells. Transcriptome analysis demonstrated that SFPQ exerts a specific function as a positive regulator of the cell cycle in melanoma, thereby promoting the expression of melanoma proto-oncogene transcripts (71). However, an alternative study from 2013 proposed that SFPQ functions as a tumor suppressor protein, binding to the promoter of the proto-oncogene Ras-related protein Rab23 (*Rab23*) to repress its transcription (72). Rab23 is a small GTPase and its overexpression has been linked to enhanced tumor migration and invasion (73). The aforementioned study demonstrated that the lncRNA Llme23 competes for binding to SFPQ, having shown that upregulation of Llme23 results in SFPQ detachment from the Rab23 promoter. This, in turn, leads to the upregulation of proto-oncogene *Rab23*, thereby exerting a pro-oncogenic effect (17,72). Therefore, SFPQ exhibits a functional duality in melanoma. While serving as an important survival factor that maintains malignant phenotypes, SFPQ concurrently exerts tumor-suppressive activity by repressing proto-oncogenes such as *Rab23*. This apparent contradiction likely stems from tumor-intrinsic heterogeneity or microenvironmental signaling variations. Future studies should integrate spatial multi-omics and conditional gene-editing technologies to decipher the molecular mechanisms governing the functional switch of SFPQ within specific molecular contexts, thereby enabling precise targeted therapeutic interventions.

In the context of transcriptional repression initiated by physiological stressors such as UV, cold shock and chemotherapy, SFPQ and NONO undergo LLPS to promote condensate formation. During formation of condensates induced by transcription inhibition, SFPQ remains associated with the active gene and connects the active chromatin to the nucleolus, thereby altering the spatial organization of the genome and increasing the number of DNA double-strand breaks (DSBs) in the active gene. The erroneous repair of these DSBs can lead to chromosomal translocations and the subsequent generation of fusion oncogenes (74).

Effects of SFPQ on cell cycle and apoptosis. The process of apoptosis, or programmed cell death, is a normal physiological process. Tumor cells achieve rapid proliferation through uncontrolled cell cycle progression and inhibition of apoptosis. Following the application of chemotherapeutic agents that promote DNA damage, tumor cells develop acquired resistance through further promotion of DNA damage repair and inhibition of apoptosis.

The depletion of SFPQ has been demonstrated to exhibit synthetic lethality in CRC cells with the BRAFV600E mutation (75). Activation of the EGFR-RAS-MAPK signaling pathway is a common occurrence in CRC (76,77). This cascade includes BRAF, a serine/threonine protein kinase belonging to the RAF kinase family. The BRAFV600E mutation results in a notable increase in the activity of this protein. This in turn results in overactivation of the MAPK pathway and the subsequent phosphorylation of nuclear transcription factors, which induces the expression of genes related to the cell cycle and cell proliferation. Additionally, the MAPK pathway induces the phosphorylation of a variety of intracellular kinases, thereby influencing cell proliferation and adhesion. However, in the course of clinical treatment, the use of RAF or MEK inhibitors often results in the development of resistance through the reactivation of the MAPK pathway (78).

To overcome this resistance, a previous study identified a synthetic lethality effect mediated by SFPQ deletion through the construction of lentiviral interference libraries of target proteins related to the nucleus of the MAPK pathway. One of the defining characteristics of tumors is the loss of control of the cell cycle and the accelerated proliferation of tumor cells. In such conditions, the error rate of DNA replication increases, as does the tolerance for replication errors. This replication pressure further increases genomic instability (79). The aforementioned study indicated that in BRAFV600E-mutated CRC cells, SFPQ is necessary for cellular recovery from replication stress. When SFPQ is depleted, the collision of DNA replication with RNA transcription, resulting in the formation of R-loops, is increased, checkpoint kinase-1 (Chk1) downstream of serine/threonine-protein kinase ATR (ATR) is phosphorylated and a notable number of tumor cells are stalled in the middle of the DNA replication in the S-phase, leading to further apoptosis. The results of both *in vivo* and *in vitro* experiments have demonstrated that tumor cell growth is markedly inhibited in the presence of the BRAFV600E mutation and SFPQ depletion. The authors of the aforementioned study therefore concluded that the synthetic lethal effect of the BRAFV600E mutation in combination with SFPQ depletion could be exploited clinically to target ATR and Chk1, which are induced by SFPQ depletion in CRC cells (75).

SFPQ promotes tumor drug resistance. SFPQ has been demonstrated to influence the resistance of certain hormone-related cancers to pharmacological agents by modulating the processing of RNA. For instance, the inhibition of the androgen-androgen receptor (AR) axis has been demonstrated to effectively suppress prostate cancer. However, the majority of patients ultimately develop resistance to AR splicing variant 7 (AR-V7), which is produced by variable splicing and results in constitutive expression. By contrast, SFPQ has been shown to enhance the expression of various spliceosomal genes and mediate the production of AR-V7 (80,81). Similarly, in ER-positive breast cancer, SFPQ expression in tumor cells is upregulated after endocrine therapy. This promotes treatment resistance by mediating the nuclear translation of ERα mRNA, which increases ER expression levels (66).

Platinum-based chemotherapeutic agents represent the primary therapeutic option for patients diagnosed with ovarian cancer. However, despite the initial efficacy of this treatment, certain patients will experience tumor recurrence following treatment. The primary mechanism of platinum resistance is associated with the upregulation of DNA damage repair and the inhibition of apoptosis in tumor cells (82). To investigate this further, a study employed an unbiased gene loss-of-function screening approach to knockdown 680 genes related to DNA damage repair, the p53 signaling pathway and apoptosis. This resulted in a notable increase in the sensitivity of tumor cells to platinum chemotherapeutic agents following the knockdown of SFPQ. The expression of SFPQ was found to be upregulated in platinum-resistant clinical samples of ovarian cancer. Through pathway enrichment analysis, the study demonstrated that SFPQ regulates alternative splicing in ovarian cancer cells, specifically promoting exon 4-7 skipping of caspase-9 pre-mRNA to generate the anti-apoptotic short isoform caspase 9-s, which consequently reduces tumor cell apoptosis and contributes to platinum resistance (Fig. 4C) (83).

In previous years, an increasing number of studies have indicated that targeting ferroptosis in tumor cells represents a promising new avenue of research. However, the issue of drug resistance inevitably arises during the application of ferroptosis inducers to treat tumors. A previous study has identified the mechanism of resistance to iron death inducers in GBM. The study indicates that NF-κB activating protein recognizes the m6A site on the cystine/glutamate reverse transporter protein (SLC7A11) transcript, recruits SFPQ to splice at the transcription termination site of the transcript and retains the last exon. This process promotes the maturation of SLC7A11 mRNA and mediates the resistance of tumors to iron-death-inducing agents (84).

SFPQ has also been demonstrated to contribute to the development of chemoresistance by virtue of its involvement in the DNA damage repair process. In triple-negative breast cancer (TNBC), following etoposide treatment, SFPQ/NONO dimers form a complex with insulin-like growth factor-binding protein 3 (IGFBP-3) to participate in non-homologous end-joining repair, thereby repairing DSBs caused by the application of chemotherapeutic agents and leading to chemoresistance in TNBC. Furthermore, this repair complex is known to also include components such as epidermal growth factor receptor (EGFR) and DNA-dependent protein kinase catalytic subunit (DNA-PKcs). Critically, the pharmacological inhibition of EGFR and DNA-PKcs can impede the formation of the IGFBP-3/NONO/SFPQ repair complex. Therefore, when inhibitors targeting EGFR, DNA-PKcs and poly [ADP-ribose] polymerase are employed in combination, they synergistically inhibit the DNA damage repair process. This results in enhanced TNBC responsiveness to platinum-based drugs (85).

GBM, a highly aggressive intracranial malignancy, is commonly treated with temozolomide (TMZ) combined with radiotherapy, which notably improves patient survival outcomes. However, the majority of patients with GBM develop TMZ resistance and tumor recurrence post-treatment, and no effective therapeutic options currently exist for recurrent cases. Therefore, elucidating the molecular mechanisms driving TMZ resistance and developing novel therapeutic strategies are imperative (86). A study identified that the lncRNA uncharacterized LOC729467 (HSD52) is overexpressed in TMZ-resistant GBM cells. Through comprehensive investigations using *in vitro* assays,

intracranial xenograft models and GBM organoid systems, researchers have demonstrated that HSD52 facilitates the interaction between the RBPs SFPQ and NONO. This interaction stabilizes RNA duplexes formed between HSD52 and E3 UFM1-protein ligase 1 mRNA, leading to sustained activation of the DNA damage repair pathway and ultimately promoting TMZ resistance in GBM (87).

Furthermore, SFPQ plays an important regulatory role in cancer progression and chemoresistance as a constituent of the nuclear paraspeckle. The paraspeckle is a nuclear condensate formed by lncRNA and NEAT1 and multiple RBPs (88,89). Its discovery in HeLa cells in 2002 led to the elucidation of its composition (90). SFPQ and NONO bind to the CTD of NEAT1v2 as a heterodimer, which is important for the recruitment of other proteins by NEAT1 and is important for the formation of paranuclear (91-93). The resulting paraspeckles have been demonstrated to facilitate the retention of RNA through adenine-to-inosine editing, a post-transcriptional modification that affects the structure, stability, localization, translation and splicing of RNAs. This function allows them to effectively fine-tune gene expression under different physiological conditions (42).

An increasing number of studies have indicated that stress signals from mitochondria and stress granules result in the upregulation of NEAT1 transcription and an increased abundance of nuclear paraspeckles (94), which play a notable role in cancer development and chemoresistance (95,96). For instance, in chronic myelogenous leukemia (CML), diminished levels of the c-Myc protein are important for the survival of CML cells (97). c-Myc interacts with and represses the expression of the NEAT1 promoter, and in the context of reduced c-Myc protein levels, the transcription of NEAT1 is enhanced, leading to an increase in the formation of paraspeckle (88). SFPQ, an important component of paraspeckle, was observed to be present in a free state within the nucleus, where it inhibited free SFPQ-mediated apoptosis and promoted CML cell survival (98). The mucin 1βs ubunit (MUC1-C) in breast cancer upregulates the expression of the RBPs SFPQ, NONO and RNA-binding protein FUS (FUS), which are important for the formation of,paraspeckle through the Myc pathway. Furthermore, MUC1-C increases the expression of NEAT1 and RBPs through polybromo-associated BAF complex-mediated chromatin accessibility. It was also observed that MUC1-C co-localizes with SFPQ and FUS in the nucleus, and that the downregulation of MUC1-C resulted in a decrease in the nuclear level of SFPQ and an increase in the cytoplasmic level of SFPQ. The MUC1-C/NEAT1 pathway confers chemoresistance and promotes the cancer stem cell status of tumor cells, indicating that the formation of paraspeckle increases stemness and chemoresistance in tumor cells (99).

SFPQ as a biomarker to predict patient prognosis in multiple tumors. A comparative analysis of differentially expressed nuclear genes in NSCLC and lung fibrosis tissues revealed that SFPQ is overexpressed in NSCLC, in addition to a unique 50-kDa short isoform that is detected exclusively in the cytoplasm of lung cancer cells. Promoter analysis of SFPQ revealed the presence of three promoters upstream of SFPQ. Hypomethylation of promoter 2, which is responsible for the short isoform, may be responsible for the appearance of the short isoform in NSCLC (31). Nevertheless, further investigation is necessary to elucidate the precise function of the cytoplasmic short isoform of SFPQ in lung cancer and the specific influence of elevated SFPQ expression on lung cancer development.

In CRC, a univariate Cox regression analysis demonstrated a significant positive correlation between the expression level of SFPQ and the overall survival of patients with CRC [area under the curve (AUC), 0.901; confidence interval, 0.866-0.937] (100). Conversely, another study indicated that patients with low SFPQ expression exhibited shorter progression-free survival than patients with high SFPQ expression (101). Furthermore, using least absolute shrinkage and selection operator Cox regression followed by multivariate Cox proportional hazards analysis, researchers identified an eight-gene prognostic signature, including SFPQ, from DNA repair-related genes in 1,096 patients with breast cancer. This model demonstrated significant predictive value for overall survival (3-year AUC, 0.708; 5-year AUC, 0.704) in the training cohort after adjusting for potential confounders through multivariate analysis (102).

4. Summary and discussion

The current review discussed the effects of SFPQ on tumor progression and drug resistance (Table I). In general, SFPQ can be used as an independent predictor of prognosis in specific tumor types, such as CRC. Additionally, SFPQ has been observed to exert oncogenic or pro-oncogenic effects in various tumors and under different environmental conditions. From a mechanistic perspective, SFPQ affects the transcriptional activity of genes by binding to histone-modifying enzymes in the nucleus or directly to DNA, thereby playing an important role in regulating the splicing, modification and localization of mRNA.

It is noteworthy that SFPQ plays a role in the formation of nuclear paraspeckles through LLPS. This process is associated with tumor stemness and drug resistance, as it affects protein abundance under stress conditions, including through RNA retention. Concurrently, the prevalence of paraspeckles exerts an influence on the quantity of free SFPQ within the nucleus, consequently impacting the function of SFPQ in the regulation of transcription on chromatin. It is therefore evident that the specific impact of SFPQ on tumor cells cannot be generalized; rather, a comprehensive analysis of the distribution of SFPQ in the nucleus, as well as the regulation of its function and localization by post-translational modifications of SFPQ itself, is required.

The RBP NONO is well-documented to exert its biological functions through heterodimerization with SFPQ. Accumulating evidence indicates that NONO is frequently upregulated in tumor tissues, where it acts as an oncoprotein to drive tumorigenesis via diverse molecular mechanisms. Previous studies have challenged the paradigm of functional synergy between NONO and SFPQ, revealing context-dependent antagonistic roles of these two proteins. The precise functional interplay and molecular basis underlying their cooperative or opposing activities remain to be fully deciphered (33,63).

Table I. Summary of the roles and mechanisms of SFPQ across various cancers.

First author, year	Cancer type	Mechanism	Regulation level	(Refs.)
Xiao *et al*, 2024	HCC	Isolates Smad4 from the Smad complex; inhibits TGF-β signaling	Transcription	(33)
Hu *et al*, 2020	HCC	Exons contain bridging integrator 1	Post-transcription	(57)
Bernard *et al*, 2021	HCC	Interferon regulatory factor 1 splicing variant 7 alternative splicing	Post-transcription	(58)
Zhang *et al*, 2022	HCC	SFPQ promotes mRNA splicing and upregulates the expression of key enzymes of glycolysis	Post-transcription	(70)
Bi *et al*, 2021	SKCM	Increases oncogene transcripts	Transcription	(71)
Zheng *et al*, 2017	SKCM	Binding of the Ras-related protein Rab23 promoter represses its transcription	Transcription	(72)
Klotz-Noack *et al*, 2020	CRC	Important for cells to recover from replication stress	DNA repair	(75)
Zhang *et al*, 2018	PDAC; CRC; non-small cell lung cancer	Mediates internal ribosome entry site translation of casein kinase 1α	Transcription	(68)
Kok *et al*, 2022	PDAC; CRC; non-small cell lung cancer	Mediates internal ribosome entry site translation of casein kinase 1α	Transcription	(29)
Gao *et al*, 2019	Kidney renal clear cell carcinoma	Forms the SFPQ/transcription factor E2F1/histone deacetylase 1 complex and downregulates solute carrier family 47 member 2 transcription	Transcription	(45)
Xie *et al*, 2021	Bladder carcinoma	Mediates exon skipping of SET domain and mariner transposase fusion gene	Post-transcription	(59)
Song *et al*, 2020	Cervical squamous cell carcinoma	Mediates substrate recognition by fat mass and obesity-associated protein	Post-transcription	(62)
Mitobe *et al*, 2020	BRCA	Facilitates the export of estrogen receptor α mRNA from the nucleus	Post-transcription	(66)
de Silva *et al*, 2019	BRCA	Forms a complex with insulin-like growth factor-binding protein 3 and mediating non-homologous end joining	DNA repair	(85)
Takayama *et al*, 2019	PRAD	Increases androgen receptor splice variant 7 through alternative splicing	Post-transcription	(80)
Takayama *et al*, 2017	PRAD	Increases androgen receptor splice variant 7 through alternative splicing	Post-transcription	(81)
Pellarin *et al*, 2020	Ovarian carcinoma	Increases anti-apoptotic splicing forms of caspase	Post-transcription	(83)
Sun *et al*, 2022	GBM	NF-κB activating protein recognizes m6A of solute carrier family 7 member 11, recruiting SFPQ to promote the maturation of pre-mRNA	Post-transcription	(84)
Dong *et al*, 2021	GBM	SFPQ relocates from C-X-C motif chemokine ligand 8 promoter to paraspeckle and upregulates IL8	Transcription	(53)

HCC, hepatocellular carcinoma; SKCM, skin cutaneous melanoma; CRC, colorectal carcinoma; PDAC, pancreatic ductal adenocarcinoma; BRCA, breast cancer; PRAD, prostate adenocarcinoma; GBM, glioblastoma; SFPQ, proline- and glutamine-rich splicing factor; TGF-β, transforming growth factor β; m6A, N6-methyladenosine.

As detailed in the present review, SFPQ exhibits both DNA- and RNA-binding activities and interacts with a range of proteins. Consequently, it primarily functions as a molecular scaffold in the nucleus, influencing gene expression by coordinating the binding of diverse RNAs, DNAs and proteins. Additional investigation is required to elucidate the way SFPQ responds to disparate external stimuli, including hypoxia and stress, in order to achieve precise nuclear localization and facilitate binding to various proteins, thereby exerting differential regulatory effects on gene expression.

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Competing interests

The authors declare that they have no competing interests.

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