Biological functions and clinic significance of SAF-A (Review)

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Abstract. As one member of the heterogeneous ribonucleoprotein (hnRNP) family, scaffold attachment factor A (SAF-A) or hnRNP U, is an abundant nuclear protein. With RNA and DNA binding activities, SAF-A has multiple functions. The present review focused on the biological structure and different roles of SAF-A and SAF-A-related diseases. It was found that SAF-A maintains the higher-order chromatin organization via RNA and DNA, and regulates transcription at the initiation and elongation stages. In addition to regulating pre-mRNA splicing, mRNA transportation and stabilization, SAF-A participates in double-strand breaks and mitosis repair. Therefore, the aberrant expression and mutation of SAF-A results in tumors and impaired neurodevelopment. Moreover, SAF-A may play a role in the anti-virus system. In conclusion, due to its essential biological functions, SAF-A may be a valuable clinical prediction factor or therapeutic target. Since the role of SAF-A in tumors and viral infections may be controversial, more animal experiments and clinical assays are needed.

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Abbreviations: AS, alternative splicing; AS1, antisense RNA 1; BER, base excision repair; CTD, C-terminal domain; DDX5, dead box helicase 5; DG, DNA glycosylase; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; DSBs, double-strand breaks; HPSE, heparanase; hnRNP, heterogeneous ribonucleoprotein; ID, intellectual disability; IR, ionizing radiation; lncRNAs, long non-coding RNAs; LIMD1, LIM domains-containing 1; MAR, matrix association region; MM, multiple myeloma; MT, microtubule; NHEJ, non-homologous end joining; NEIL, Nei endonuclease VIII-like; PCAF, p300/CBP-associated factor; Pol II, RNA polymerase II; SAF-A, scaffold attachment factor A; SAP, SAF/Acinus/PIAS; TADs, topologically associating domains; TNF α, tumor necrosis factor α; VEGF, vascular endothelial growth factor; VSV, vesicular stomatitis virus

Key words: SAF-A, chromatin organization, transcription, RNA metabolism, DNA repair, mitosis

Contents

1. Introduction

Scaffold attachment factor A (SAF-A), or heterogeneous ribonucleoprotein U (hnRNP U), belonging to the hnRNP subfamily, is an abundant component of nuclear matrix and hnRNP particles (1).

The human *SAF-A* gene, located on chromosome 1 q44, has 2 transcript variants, in which variant 2 lacks a segment in the coding region compared with variant 1 (2). Consequently, this causes two isoforms with different lengths, yet the same reading frame.

Since human SAF-A (Uniprot code: Q00839) contains 825 amino acids, its predicted molecular weight is ~90 kDa. But, due to modifications such as phosphorylation, SAF-A is usually observed to be ~120 kDa. SAF-A is widely expressed in various organs or tissues, such as bone marrow, lymphoid tissues, brain, heart, lung and kidney (https://www.proteinatlas.org/ENSG00000153187-HNRNPU). Due to its functional domains, SAF-A binds to both DNA (such as scaffold-attached region DNA) and RNA (such as chromatin-associated RNAs) and plays essential roles in several cellular processes such as chromatin structure regulation (3), transcription (4) and mitosis (5). The present review summarized the structure, multiple functions and clinical significance of SAF-A.

2. Materials and methods

The present narrative review was performed by screening the Pubmed (https://pubmed.ncbi.nlm.nih.gov/), Medline (https://www.nlm.nih.gov/medline/medline_overview.html) and Google Scholar (https://scholar.google.com/) databases using the key words: 'hnRNPU', 'SAF-A', 'chromatin organization', 'transcription', 'RNA metabolism', 'DNA repair', 'mitosis', 'tumor', 'neurodevelopment', and 'anti-virus'. Published between 2014 and 2024, the English-written articles available with a full text were mainly used, and these articles were involved in animal and human studies.

3. The structure of SAF-A

SAF-A contains three domains: N-terminal DNA-binding, C-terminal RNA binding and middle domain (6-8) (Fig. 1). Notably, the DNA-binding domain SAF/Acinus/PIAS (SAP) is important for interaction with matrix association region (MAR) in chromatin (6). Containing a cluster of arginine/glycine-rich (RGG) repeats, the C-terminus of SAF-A is necessary for binding to inactive X chromosome regions and chromatin-associated RNAs (8). The middle domain of SAF-A, including an SPla and RYanodine receptor and a nucleotide triphosphate hydrolase region (9,10), mediates its interaction with different proteins, such as forkhead box N3 (11), Wilms' tumor suppressor gene 1 (9) and severe fever with thrombocytopenia syndrome virus nucleocapsid protein (12).

4. Functions of SAF-A

SAF-A participates in chromatin organization. In the eukaryotic cell nucleus, chromatin forms 3-D structures at multiple levels, including domains, loops, A and B compartments (relating to active and inactive chromatin, respectively), topologically associating domains (TADs) and territories (13-16).

In early research, SAF-A was found to form large aggregates *in vitro* and induce DNA loops to gather around them (17) (Fig. 2A). When SAF-A is depleted in mouse hepatocytes, lamina-associated domains increase, compartments switch, TAD boundary strengthens, and chromatin loop intensities decrease, demonstrating that SAF-A plays a vital role in maintaining the higher-order chromatin organization (18).

Further studies demonstrated that SAF-A regulates chromatin structure via RNA. Jiao *et al* (19) found that SAF-A binds to histone acetyltransferases p300 in cancer cells (19). Facilitated by heparanase (HPSE) enhancer RNA, the SAF-A-p300 complex is enriched on the super-enhancer, consequently leading to chromatin looping between the *HPSE* promoter and the super-enhancer. Consistently interacting with chromatin-associated RNAs, SAF-A forms oligomerization that induces de-compaction of large-scale human interphase chromatin structure (8) (Fig. 2A). In this way, SAF-A maintains genomic stability (8). When human monocyte THP-1 cells are infected by vesicular stomatitis virus (VSV), SAF-A interacts with viral infection-induced RNAs, mediating the openness and activation of antiviral immune genes (20). Puvvula and Moon (10) treated cancer cells with cell-penetrating peptides derived from SAF-A, and found that the SAP-derived peptide rather than the RGG-derived one promotes chromatin compaction in HCT116 (colorectal), T47D (breast) and UMUC3 (bladder) cancer cells. Based on these observations, RNA is proposed to be essential for SAF-A-induced chromatin de-compaction.

Besides RNA, DNA was also reported to be necessary for SAF-A to regulate chromatin structure. In the study of Kolpa *et al* (21), similar to the C280 SAF-A deletion mutant (only containing RGG domain), the expression of ΔRGG (containing DNA-binding domain) and G29A mutants (in lack of DNA-binding ability) was able to release C0T-1 RNA from chromatin, resulting in chromatin condensation. Despite this, their regulatory mechanism is different. ΔRGG SAF-A mutant mainly replaced endogenous SAF-A from chromatin, while the G29A mutant still combined with C0T-1 RNA and could not bind to chromatin (21). Therefore, to some degree, SAF-A may play a role in bridging C0T-1 RNA and chromatin to regulate chromatin architecture. Depending on the SAP domain, SAF-A was also found to combine with MARs and the pericentromere tandem repeats in chromocenters (6,22). Therefore, it was hypothesized that SAF-A tethers MARs to the chromocenter to organize nuclear architecture (1).

SAF-A regulates transcription. In eukaryotic cells, transcription of protein-coding genes, including initiation, elongation and termination phases, contains numerous regulatory proteins affecting either the RNA polymerase II (Pol II) machinery or chromatin structure (23-26).

Previous studies have indicated that SAF-A is involved in initial transcriptional regulation. Actin in the nucleus regulates transcription by remodeling chromatin, regulating transcription factor (TF) location, or binding to RNA polymerase (27-30). Through extracellular vesicles derived from embryonic stem cells, SAF-A is transferred into human coronary artery endothelial cells to combine with actin. The SAF-A-actin complex leads to enhanced RNA Pol II phosphorylation and its level on vascular endothelial growth factor (*VEGF*) promoter, upregulating VEGF expression (4) (Fig. 2B). When the SAF-A-actin complex is disrupted by H19 [a long non-coding (lnc) RNA], the phosphorylation of the Pol II C-terminal domain (CTD) is inhibited, and consequently, Pol II-mediated transcription is prohibited (31). Additionally, SAF-A was found to associate with elements within the promoter regions. In Sertoli cells, SAF-A has been identified to bind directly to the promoter regions of *Sox8* and *Sox9*, thereby enhancing their expression (32) (Fig. 2B). Similarly, IL21-anti-sense RNA 1 interacting with SAF-A binds to the *IL21* promoter, which is essential for regulating IL21 transcription (33). Research on embryonic stem cells also revealed that not only does SAF-A bind to the *Oct4* proximal promoter, but it also interacts with endogenous Pol II. And depletion of SAF-A impairs Oct4 expression (34).

In previous studies, SAF-A appeared to have two-way adjusting effects on transcription elongation mediated by Pol II. According to the study of Obrdlik *et al* (35), SAF-A, actin and p300/CBP-associated factor (PCAF) were associated with the phosphorylated Pol II CTD; and the actin-SAF-A interaction assisted Pol II transcription elongation depending on PCAF (Fig. 2B). On the contrary, in another study, SAF-A inhibited Pol II elongation. Through the middle domain, SAF-A was sufficient to combine with Pol II and repressed TF IIH-mediated Pol II CTD phosphorylation, which inhibited Pol II elongation (36) (Fig. 2B).

Figure 1. Structural schematic diagram of SAF-A. The N-terminal SAP motif is necessary for DNA binding. Dependent on the SPRY domain, SAF-A binds to other proteins. The NTP hydrolase domain of SAF-A mediates ATP binding and hydrolysis. In the C-terminus, the RGG region combines with RNA and ssDNA (8,10). SAF-A, scaffold attachment factor A; SAP, SAF/Acinus/PIAS; SPRY, SPla and RYanodine receptor; NTP, nucleotide triphosphate; RGG, arginine/glycine-rich.

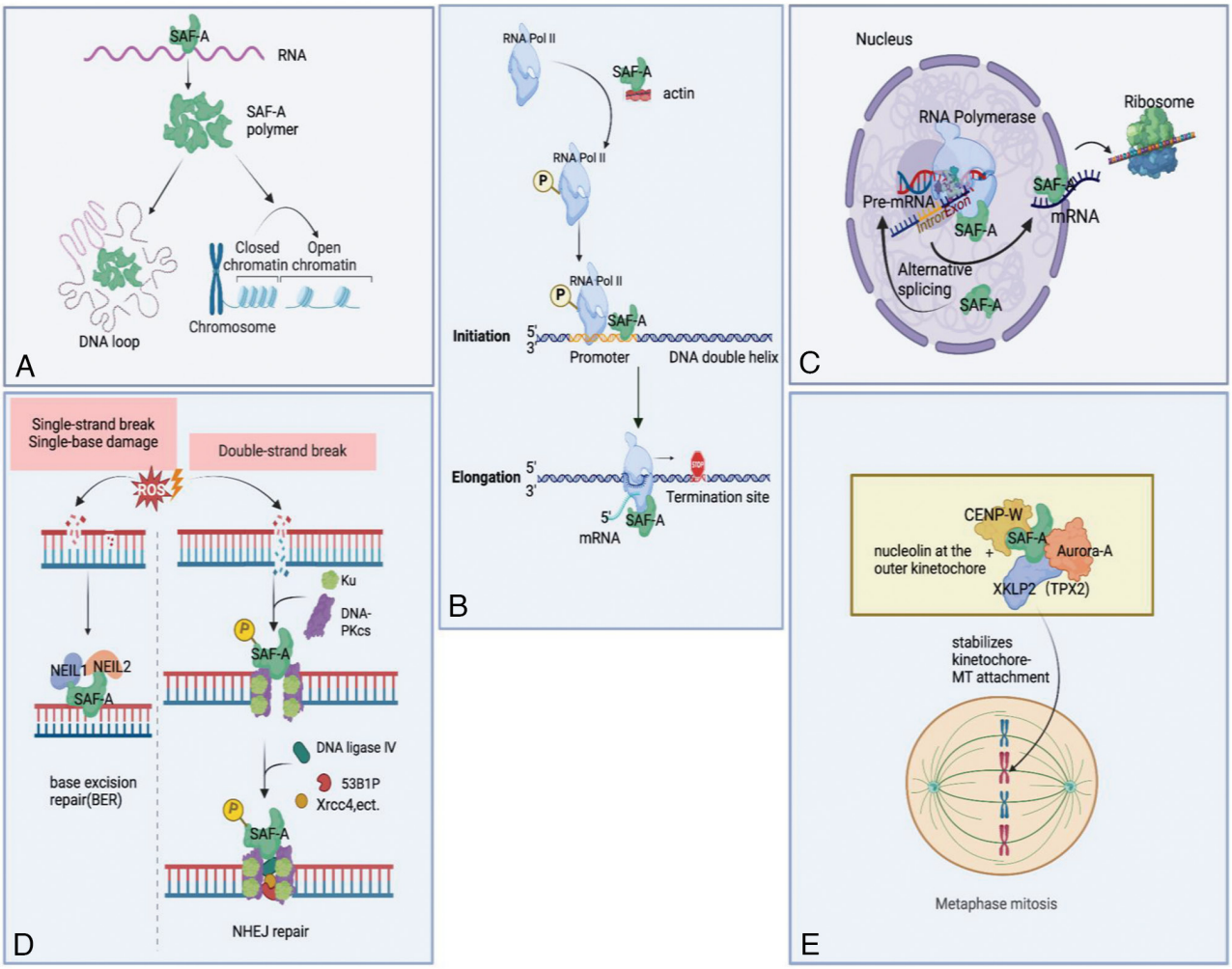

Figure 2. Functions of SAF-A. (A) Binding to RNA, SAF-A promotes DNA loop formation (17). Through consistent interaction with chromatin-associated RNAs, SAF-A forms oligomers to induce de-compaction of the large-scale human interphase chromatin structure (8). (B) During transcription initiation, SAF-A-actin interaction enhances RNA Pol II phosphorylation (4). Besides, SAF-A binds to elements within promoter regions to promote transcription (32). During the elongation of transcription, SAF-A interacts with RNA pol II to modulate transcription (35,36). (C) SAF-A participates in the selective splicing of pre-mRNA and stabilizes mRNA during their transportation (39). (D) Interacting with NEIL1 and NEIL2, SAF-A participates in oxidized base lesions through DG repair (50). When double-strand breaks are induced, SAF-A is recruited and phosphorylated at Ser59 to promote NHEJ repair mediated by Ku, DNA-PKcs and XRCC4 (54,55,58). (E) During mitotic metaphase, SAF-A stabilizes not only the interaction between kinetochore and kinetochore-MT but also CENP-W through binding to it (61,62). The image was generated using the online platform https://www.biorender.com. SAF-A, scaffold attachment factor A; RNA Pol II, RNA polymerase II; NEIL, Nei endonuclease VIII-like; NHEJ, non-homologous end joining; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; XRCC4, X-ray repair cross-complementing protein 4; MT, microtubule; CENP-W, centromere protein W.

SAF-A plays roles in RNA metabolism. SAF-A has also been implicated in various aspects of RNA metabolism, including normal and alternative pre-mRNA splicing and RNA transporting (Fig. 2C).

Ye *et al* (37) inactivated SAF-A expression in murine hearts and found that compared with wild type, SAF-A mutant in hearts results in extensive intron retention and cassette skipping. In contrast to the wild-type samples, mouse cortices with SAF-A mutations showed 850 differentially spliced genes, and the gene splicing included exon skipping, an alternative 3' or 5' splice site and intron retention (38).

Then, by what mechanism does SAF-A regulate pre-mRNA splicing? Xiao *et al* (39) found that SAF-A binds to all the small nuclear RNAs essential for splicing major and minor intron classes and regulates U2 small nuclear ribonucleoprotein maturation and Cajal body morphology. However,

Vu *et al* (40) demonstrated the different splicing regulatory mechanisms of SAF-A. Competed with hnRNP L (a splicing repressor) to combine with an RNA *cis*-element in the exon 3 of caspase-9, SAF-A promotes the exon 3, 4, 5, 6 cassette inclusion in the mature caspase-9 mRNA, determining the preferential expression of caspase-9a rather than caspase-9b.

It has been identified that SAF-A is responsible for transporting and stabilizing mRNA via directly binding to it. Zhao *et al* (41) found that SAF-A binds to tumor necrosis factor α (*TNF-α)*, *IL-6* and *IL-1β* mRNAs and that down-regulation of SAF-A expression in macrophages induces the decreased half-life of these cytokine mRNAs. Besides, Toll-like receptor signaling in macrophages leads to SAF-A translocation from nuclear to cytoplasm (41). During this translocation, SAF-A is proposed to stabilize pro-inflammatory cytokine mRNAs (41). In agreement with the aforementioned study, SAF-A was found to bind to the 3' untranslated region of *TNF α* mRNA to stabilize it and specifically enhance TNF α expression (42). However, other studies suggested that SAF-A stabilizes mRNA depending on other molecules. Pan *et al* (43) found that interaction between LIM domains-containing 1 antisense RNA 1 (LIMD1-AS1) and SAF-A is essential for stabilizing *LIMD1* mRNA in non-small cell lung cancer. Furthermore, Lu *et al* (44) reported that following lipopolysaccharide stimulation in human intestinal epithelial cells, functional intergenic repeating RNA element cooperating with SAF-A may regulate the stabilization of vascular cell adhesion protein 1 and *IL12p40* mRNAs through targeting the AU-rich elements of these mRNAs.

SAF-A repairs both oxidized lesions and double-strand breaks (DSBs). In cells, ionizing radiation (IR) and reactive oxygen species may result in clustered oxidized bases and DSBs that are also induced by V(D)J recombination (45-47). Oxidized base lesions in the human genome are repaired via DNA glycosylase (DG) repair, also known as base excision repair (BER). Repair enzymes, including Nei endonuclease VIII-like (NEIL) and certain non-repair proteins, such as SAF-A, initiate this process (48,49). In previous studies, SAF-A was demonstrated to interact directly with NEIL1 and stimulate NEIL1-mediated repair of oxidative base damage (48,49). In addition to NEIL1, SAF-A combines with NEIL2, enhancing NEIL2-initiated transcribed gene-specific repair of oxidized bases (50) (Fig. 2D).

However, BER of bi-stranded oxidized bases can lead to additional DSBs, causing loss of DNA fragments. This may be avoided if DSBs are repaired through non-homologous end joining (NHEJ) mediated by Ku, DNA-dependent protein kinase catalytic subunit (DNA-PKcs), X-ray repair cross-complementing protein 4 (XRCC4), DNA ligase IV, and cernunnos-XRCC4-like factor complex, preceding BER (51-53). In response to irradiation-induced DSBs, SAF-A is rapidly recruited to DNA damage sites (54) (Fig. 2D). Besides, DSBs cause phosphorylated SAF-A at Ser59, which is exclusively dependent on DNA-PK (55,56) (Fig. 2D). In NHEJ-deficient cells treated with IR or clastogenic drugs, the extent and duration of SAF-A phosphorylation at Ser59 increase (56), which suggests that phosphorylated SAF-A may be a biomarker for testing the capacity of the cells to repair DSBs by NHEJ. A previous study showed that SAF-A phosphorylation at Ser59 is related to transient NEIL1 release from chromatin and BER prevention. Then, due to dephosphorylation, SAF-A reactivates BER by relieving DG inhibition (57). These results suggested that DSB repair by NHEJ or BER is partly determined by whether SAF-A is phosphorylated. However, a recent study found that increased SAF-A stabilizes or recruits NHEJ factors via liquid-liquid phase separation, including Ku80, 53BP1, DNA-PKcs and the shieldin complex at DSBs during antibody class-switch recombination (58) (Fig. 2D). The finding supplies SAF-A may balance between BER and NHEL through complex mechanisms.

SAF-A takes part in mitosis. During mitosis, kinetochore-microtubule (MT) attachment and chromosome congression at the spindle equator is essential to accurate chromosome segregation (59,60). Interestingly, SAF-A binds to not only Aurora-A and targeting protein for Xklp2 (TPX2) at spindle MTs, but also nucleolin at the outer kinetochore, whereby SAF-A stabilizes kinetochore-MT attachment (61) (Fig. 2E). Via non-coding RNA, SAF-A interacts with centromere protein W (CENP-W, an inner centromere component crucial for forming a functional kinetochore complex). Notably, SAF-A-CENP-W interaction increases their stability, and they co-localize at the MT-kinetochore interface during mitosis (62) (Fig. 2E). Furthermore, SAF-A depletion in cells leads to delayed mitosis, unsuccessful chromosome alignment, and spindle assembly (61).

In addition, SAF-A is dynamically phosphorylated during mitosis, and in human cells, phosphorylation at serine 2 (S2), S3, S4, S59, S66 and S270 is related to mitosis (63-65). Douglas *et al* (66) found SAF-A is phosphorylated at S59 by polo-like kinase 1 instead of DNA-PK and is dephosphorylated by protein phosphatase 2A. Mutations of SAF-A S59 in cells lead to aberrant mitoses, including polylobed nuclei, delayed passage, misaligned and lagging chromosomes (66). However, the regulatory mechanism of phosphorylated SAF-A on mitosis remains elusive.

5. Clinical significance of SAF-A

SAF-A is associated with tumor development and resistance to chemotherapy. Previous studies revealed that SAF-A mainly promotes proliferation (67-71), aggressiveness (19) and migration (71) of tumors (Table I). SAF-A is overexpressed in hepatocellular carcinoma or acute myeloid leukemia, and the proliferation of these tumors is inhibited *in vitro* and *in vivo* due to SAF-A downregulation (68-70). Further studies demonstrated that SAF-A promotes tumor proliferation through combining with lncRNAs, such as promoter of CDKN1A antisense DNA damage activated RNA (*PANDA*) in esophageal squamous cell carcinoma and hepatocyte nuclear factor 4 alpha-AS1 in neuroblastoma (67,69). Jiao *et al* (19) also used several cancer cell lines and found that SAF-A interaction with *HPSE* enhancer RNA enhances HPSE expression and activity, which promotes tumorigenesis and aggressiveness. In the research of Han *et al* (71), SAF-A was found to interact with dead box helicase 5 (DDX5) to promote the proliferation and migration of triple-negative breast cancer. On the one hand, the SAF-A-DDX5 complex leads to alternative splicing

Table I. The roles of SAF-A in various cancers.

System	Cancer type	The roles of SAF-A	(Refs.)
Digestive	Gastric carcinoma	SAF-A is involved in the development of gastric cancer by regulating alternative splicing	(72)
	HCC	SAF-A promotes HCC development by enhancing CDK2 transcription	(68)
	Esophageal squamous cancer	Long non-coding RNA *PANDA* binds to SAF-A to promote tumor proliferation through the CyclinD1/2-Cyclin E1 and Bcl-2 pathways	(67)
Respiratory	Non-small cell lung cancer, lung squamous cell carcinoma	SAF-A can inhibit tumor proliferation and enhance the sensitivity of lung squamous cell carcinoma to cisplatin	(43,78)
Urinary system	Bladder carcinoma	SAF-A can interact with family with sequence similarity 171 B, an independent predictor of bladder cancer progression, and regulate the CCL2 pathway to promote cancer progression. Knocking down SAF-A can increase the sensitivity of bladder cancer to cisplatin	(75,76)
	Renal cell carcinoma	A combination of SAF-A and piRNA-1742 stabilizes *USP8* mRNA or regulates alternative splicing to promote the progression of renal cell carcinoma	(73,74)
Reproductive system	Triple-negative breast cancer	Interaction between SAF-A and dead box helicase 5 promotes the proliferation and migration of triple-negative breast cancer	(71)
Blood system	MM	Knockdown of SAF-A increases MM sensitivity to selinexor	(77)

SAF-A, scaffold attachment factor A; HCC, hepatocellular carcinoma; MM, multiple myeloma.

(AS) of minichromosome maintenance protein 10 pre-mRNA and subsequent activation of Wnt/β-catenin signaling. On the other hand, the complex enhances the expression of LIM domain only protein 4 by locating in its transcriptional start sites, activating PI3K-Akt-mTOR signaling (71). Regulating AS, SAF-A is involved in the pathogenesis of gastric cancer and renal clear cell carcinoma (72,73). Zhang *et al* (74) found that SAF-A also binds to P-element-induced wimpy testis-interacting RNA-1742 (piRNA-1742) to stabilize *USP8* mRNA and promote the progression of renal cell carcinoma. Through interaction with a family with sequence similarity 171 B (an independent prognostic factor for bladder cancer progression), SAF-A regulates the CCL2 pathway to facilitate M2 macrophage polarization in the tumor microenvironment, thereby promoting bladder cancer development (75).

Further studies have demonstrated a correlation between SAF-A and resistance to chemotherapy. Shi *et al* (76) discovered that the knockout of SAF-A in human T24 cells enhances bladder cancer susceptibility to cisplatin via inhibition of cell proliferation and impairment of cellular invasion and migration capabilities. In the research of Wang *et al* (77), the knockdown of SAF-A increases selinexor sensitivities of multiple myeloma (MM) cells *in vitro* and in mouse models and MM patients with relatively low SAF-A expression response to selinexor.

However, a few studies demonstrated that SAF-A might suppress tumor cell proliferation and enhance sensitivities to chemotherapy. Pan *et al* (43) reported that LIMD1 inhibits proliferation and promotes apoptosis in non-small cell lung cancer cells, and SAF-A interacts with lncRNA *LIMD1-AS1* to stabilize *LIMD1* mRNA. Puvvula and Moon (10) dealt with various tumor cells with SAF-A RGG- or SAP-derived peptides. Depending on different mechanisms, these peptides suppress breast, bladder, colorectal and prostate cancer cell proliferation. The SAF-A RGG-derived peptides mainly alter SAF-A splicing and binding targets, while the SAP-derived regulates global epigenetic marks to induce DNA damage reaction and cell death (10). Li *et al* (78) also identified that lncRNA *SFTA1* could augment cisplatin sensitivity in treating lung squamous cell carcinoma by upregulating SAF-A.

The contradictory effects of SAF-A on tumors may result from different tumor types or test methods. Therefore, more animal and clinical experiments are needed to identify its functions further.

SAF-A participates in proviral or antiviral response. Previous research revealed that SAF-A plays dual roles in antiviral response. Through the N-terminal fragment (aa1-86), SAF-A targets the 3' long terminal repeat of human immunodeficiency virus type 1 mRNA and blocks viral replication in cells (79). Furtherly, in both *in vitro* and *in vivo* animal experiments, SAF-A has been reported to be associated with the initiation of innate immunity against viruses, including severe fever with thrombocytopenia syndrome virus, VSV, and herpes simplex virus type 1 by recognizing nuclear or cytoplasmic viral RNA (12,20,80).

However, Gupta *et al* (81) found that SAF-A is associated with the leader RNA of VSV and co-localizes with the virus in the cytoplasm of infected cells, implying that SAF-A may contribute to the life cycle of VSV and its pathogenesis. In recent studies, SAF-A was found to negatively regulate innate immune responses against infectious bursal disease viruses and porcine epidemic diarrhea virus and induce immune escape of these viruses (82,83).

Therefore, the diverse roles of SAF-A played in these experiments may be due to different viruses or hosts, and more animal experiments are needed to determine the roles of SAF-A in antiviral immunity.

SAF-A links to neurodevelopment. Caliebe *et al* (84) first revealed that patients with a chromosome deletion 0.440 Mb in region 1q44 bearing *SAF-A* suffer from seizures and speech delay. Similarly, Depienne *et al* (85) reported that 1q43q44 containing *SAF-A* microdeletion leads to intellectual disability (ID) and epilepsy. Employing molecular genetic testing, a series of pathogenic *SAF-A* mutants have been identified to be associated with developmental delay and neurodevelopmental disorder showing severe ID with delay of speech and language, early-onset seizures, and autistic features as well (85-90). Despite this, the regulatory mechanism of SAF-A on neurodevelopment remains elusive. In a recent study, deletion of SAF-A in cultured neural progenitors and murine brains resulted in varied gene expression and AS, apoptosis of neural cells and abnormalities in neuronal migration, suggesting that SAF-A is essential for the development of cortex (38).

6. Conclusions

SAF-A is one of the main components of the nuclear matrix. Capable of binding both DNA and RNA, SAF-A has crucial functions in regulating chromatin architecture, transcription, RNA metabolism, DNA repair and mitosis. Humans or mice with SAF-A deficiency or mutants display embryonic death (91), lethal cardiomyopathy (37) and neurodevelopmental disorders (38,90). Therefore, SAF-A may be a valuable prediction factor or therapeutic target. Besides, SAF-A has been observed to be related to anti-infection and tumor progression, though these functions are controversial. Because of this, more animal experiments and clinical assays are needed.

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Availability of data and materials

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Authors' contributions

XC, ML and DZ contributed to the conception of the study. DZ and LL performed the literature research and wrote the manuscript. XC and ML revised the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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