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Review

Application of stress granule core element G3BP1 in various diseases: A review

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ABSTRACT

Ras-GTPase-activating protein-binding protein 1 (G3BP1) is a core component and crucial regulatory switch in stress granules (SGs). When the concentration of free RNA within cells increases, it can trigger RNA-dependent liquid-liquid phase separation (LLPS) with G3BP1 as the core, thereby forming SGs that affect cell survival or death. In addition, G3BP1 interacts with various host proteins to regulate the expression of SGs. As a multifunctional binding protein, G3BP1 has diverse biological functions, influencing cell proliferation, differentiation, apoptosis, and RNA metabolism and serving as a crucial regulator in signaling pathways such as Rac1-PAK1, TSC-mTORC1, NF-κB, and STAT3. Therefore, it plays a significant role in the regulation of neurodegenerative diseases, myocardial hypertrophy, and congenital immunity, and is involved in the proliferation, invasion, and metastasis of cancer cells. G3BP1 is an important antiviral factor that interacts with viral proteins, and regulates SG assembly to exert antiviral effects. This article focuses on the recent discoveries and progress of G3BP1 in biology, including its structure and function, regulation of SG formation and dissolution, and its relationships with non-neoplastic diseases, tumors, and viruses.

1. Introduction

Recent studies have shown that biomolecular condensates play crucial roles in controlling various biological functions. Biomolecular condensates are formed when molecules inside the cell aggregate through multivalent weak interactions, undergoing a phase separation to create substances resembling "droplets" [1]. This process is assembled through liquid-liquid phase separation (LLPS), which is a specific phenomenon in which RNA and RNA-binding proteins (RBPs) collectively form these droplets [2]. Several nucleic acids exhibit a similar multivalent "sticker-and-spacer" configuration [3], whereas RBPs possess low-complexity domains (LCDs) [4]. These features facilitate the formation of droplet-like structures in aqueous environments, a process known as LLPS [5].

Stress granules (SGs) are a prominent type of biomolecular condensate, and dynamic and reversible cytoplasmic assemblies are formed in response to stress in eukaryotic cells. Their composition primarily includes translation initiation factors, mRNA, 40S ribosomal subunits, and several crucial RBPs [6,7]. The primary factors influencing SG assembly through LLPS are unevenly distributed interactions within the core protein-RNA network. The center of this network is the multifunctional Ras-GTPase-activating protein binding-protein 1 (G3BP1) [8,9]. As a molecular switch, G3BP1 responds to the concentration of free RNA within cells, triggering RNA-dependent LLPS as the concentration increases. Ras-GTPase-activating protein-binding proteins encompass a series of RBPs, including G3BP1 and G3BP2 in mammals [10]. Despite the high similarity in amino acid sequences and protein structures of G3BP1 and G3BP2, they exhibit significantly different biological functions [11]. G3BP1, a multifunctional binding protein with a molecular weight of 68 kDa, primarily expresses in the cytoplasm, while also possessing the ability to enter the cell nucleus. In recent years, researchers have gradually discovered various biological functions of G3BP1. It can influence cell proliferation, migration, apoptosis, differentiation, and RNA metabolism [8,12–16]. As a crucial regulator of cellular RNA metabolism, it plays a significant role in axonal translation, ribosomal quality control, transcriptional downturn, and other cellular

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processes [17–22].

G3BP1 is a crucial SG component that interacts with various host proteins to regulate SG formation [8,23]. In addition, it functions as an antiviral factor by interacting with viral proteins and modulating SG assembly to exert antiviral effects [24–27]. However, several viruses exploit G3BP1 as a proximal factor to recruit translation initiation factors, thereby promoting viral replication [28–30]. Because of its ability to regulate gene expression by modulating mRNA translation and decay, G3BP1 is closely associated with diseases such as cancer, atherosclerosis, neurodevelopmental disorders (NDDs), and testicular spermatogenic dysfunction [31–39]. Furthermore, as a key regulator of cellular RNA metabolism, G3BP1 plays a crucial role in processes such as axonal translation, ribosomal quality control, and transcriptional downturn [14,15,40–42]. However, the classic function of G3BP1 is its response to environmental stress, promoting the assembly of SGs in the cytoplasm of eukaryotic cells to alter their survival under conditions of damage [23,43]. This article focuses on recent discoveries and advances in the field of biology regarding G3BP1, including its structure and expression regulation, role in SG assembly and disassembly, and involvement in alterations of SG pathways in non-tumor diseases, tumors, and viruses. These findings enrich the current review centered on G3BP1 and SGs, aiming to provide support for targeted research on its implications in diseases and viruses.

2. Structure and function of G3BP1

1. G3BP1 structure

G3BP is known for its ability to bind and recognize the SH3 domain of the Ras-GTPase-activating protein (Ras-GAP) [11]. In mammals, the G3BP family consists of three homologous proteins: G3BP1, G3BP2a, and its splice variant, G3BP2b [44]. G3BP1 contains four important domains: the nuclear transport factor 2 domain (NTF2); intrinsically disordered region 1 (IDR1), which is highly negatively charged and acidic; intrinsically disordered region 2 (IDR2), which has a slightly positive charge; and the RNA-binding domain (RBD). RBD is composed of an RNA recognition motif (RRM) and an arginine-glycine-rich region (such as IDR3) (Fig. 1). The NTF2-like domain, RNA-binding domain, and intrinsically disordered regions are crucial for mediating essential protein-RNA interactions [45].

2. The functions of G3BP1

2.1 Involved in DNA, RNA, and protein regulation

Cyclic GMP-AMP synthase (cGAS), a cellular DNA sensor, plays a crucial role in innate immunity [46]. In 2022, Zhao et al. discovered that G3BP1 facilitated the entry of cGAS into primary LLPS, leading to its subsequent rapid activation. Knocking out or inhibiting G3BP1 significantly reduced DNA-induced LLPS and cGAS activation. In addition, when dsDNA was introduced into the cGAS-G3BP1 complex, cGAS rapidly concentrated with the DNA, causing its dissociation from G3BP1. In contrast, dsRNA and single-stranded RNA, while forming complexes with cGAS and G3BP1, did not trigger dissociation upon RNA stimulation. Therefore, the authors suggested that binding of the cGAS-G3BP1 complex to DNA is necessary for the dissociation of G3BP1 from cGAS [47].

RNA regulation is crucial for controlling several cellular processes [48]. In 2020, Fischer et al. reported that G3BP1 may mediate mRNA decay by recognizing base-pairing secondary structures in the 3′-untranslated region (UTR) [21]. RNA guanine quadruplexes (rG4s) are atypical four-stranded RNA structures formed in guanine (G)-rich regions in the transcriptome [49]. In 2021, He et al. discovered that G3BP1 can act as an rG4-binding protein, with its C-terminal RGG domain participating in rG4 recognition. Luciferase reporter gene assays revealed that G3BP1 positively regulates mRNA stability by binding to rG4 structures [22]. In 2022, Kim et al. showed that Bruton's tyrosine kinase (BTK) phosphorylation of G3BP1 induces G3BP1 oligomerization and promotes the condensation of RNA-protein complexes into large molecular aggregates [18]. Kirchhof et al. showed that the long non-coding RNA (lncRNA) cytoplasmic G3BP1-associated lncRNA (CALA) is an effective regulator of RNA transcription in endothelial cells. CALA forms a cytoplasmic ribonucleoprotein complex with G3BP1, thereby regulating the endothelial cell function [50].

Several proteins interact with the 5′-untranslated region (5'-UTR) of G3BP1, thereby regulating its expression. Y-box binding protein 1 (YB-1), located in SGs, can directly bind to and translationally activate the 5'-UTR of G3BP1 mRNA, thereby regulating the translation of G3BP1 [51]. In addition, in 2020, Lee et al. conducted in vitro translation experiments using a luciferase reporter and determined that melanoma antigen gene B2 (MAGE-B2) can bind to the 5'-UTR of G3BP1, promoting its translation [52].

2.2 Participation in signal transduction

Signal transduction is the foundation for the maintenance of normal activity in organisms. In 2020, Pla-Martín et al. discovered that during starvation, CLUH can inhibit mTORC1 activation and the mitochondrial synthetic metabolic pathway, while promoting mitochondrial turnover, thereby achieving effective metabolic remodeling. In addition, CLUH plays a role in signal transduction by sequestering mTOR kinase and G3BP1 [53]. In 2020, Lo et al. showed that protein arginine methyltransferase 8 (PRMT8) controls synaptic actin by methylating dendritic G3BP1 and inhibiting the Rac1-PAK1 signaling pathway, thereby promoting dendritic spine morphology [54]. In 2022, Deater et al. discovered that tudor domain-containing 3 (TDRD3), as an antiviral restriction factor, can enhance the interferon (IFN) signal transduction of G3BP1 [41].

G3BP1 is an essential protein for activating the senescent-associated secretory phenotype (SASP) [55]. In 2020, Omer et al. reported that during the aging process, G3BP1 activates the SASP by promoting the binding of cyclic GMP-AMP synthase to cytoplasmic chromatin fragments. Conversely, G3BP1 also activates the NF-κB and signal transducer and activator of transcription 3 (STAT3) pathways through cGAS, thus promoting SASP expression and secretion. Depleting G3BP1 significantly reduces the phosphorylation and nuclear localization of IκBα when promoting the activation and signal transduction required for SASP. As G3BP1 decreases, the phosphorylation of STAT3 also significantly decreases, indicating that the loss of G3BP1 reduces NF-κB and STAT3 signaling [55].

Disruption of the tuberous sclerosis complex (TSC) can lead to activation of the mechanistic target of rapamycin complex 1 (mTORC1) in TSC, resulting in diseases associated with cellular overgrowth, migration, and neuronal excitability [56]. G3BP1 anchors the TSC protein complex to lysosomes [57] and serves as a lysosomal tether for the TSC complex [58]. In 2021, Prentzell et al. demonstrated that G3BP1 does

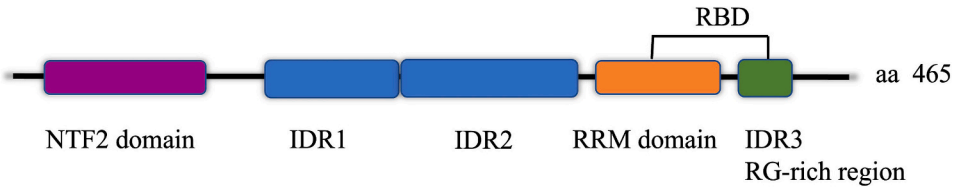

Fig. 1. G3BP1 structure. The four important functional motifs of G3BP1 include the NTF2 structural domain, IDR1 region, IDR2 region, and RBD region, comprising the RRM and arginine-glycine-rich region (such as IDR3).

not affect mTORC1 activity in cells with SGs; conversely, in the absence of SG, G3BP1 undergoes mTORC1 inhibition [58]. Therefore, G3BP1 is a critical component of lysosomal TSC-mTORC1 signaling transduction.

2.3 The role in antiviral, immune, and oxidative stress responses

G3BP1 is a key protein involved in antiviral responses [59]. It enhances the immune response against invading viruses by inducing IFN expression and translating IFN-stimulated genes (ISGs). Within virus-infected cells, G3BP1 binds to double-stranded RNA (dsRNA) generated during viral replication via its RGG domain, enhancing the expression of RIG-I-induced IFN-β mRNA. In response to changes in IFN signaling, G3BP1, G3BP2, and caprin-1 collectively promote ISG translation to synthesize antiviral factors [60]. In addition, G3BP1 can induce translation stalling by assembling SGs, thereby impeding the translation factors necessary for viral protein synthesis [24].

In 2021, Dou et al. reported that nuclear factor 90 (NF90) induces the phosphorylation of double-stranded RNA-activated protein kinase R (PKR) upon viral induction. The phosphorylation mediated by PKR and the activation of eukaryotic translation initiation factor 2α (eIF2α) form SGs, inducing the expression of G3BP1 and T-cell intracellular antigen-1 (TIA-1), thereby disrupting viral mRNA translation. In addition, the immune checkpoint inhibitor Tim-3 promotes ubiquitination and degradation of NF90, inhibiting NF90-SG-mediated antiviral immunity [26]. The E3 ubiquitin ligase tripartite motif (TRIM) family plays a significant role in antiviral restriction and innate immune regulation; TRIM25-mediated ubiquitination is particularly prominent [61]. In 2022, Yang et al. validated G3BP1 as a novel substrate for TRIM25, and their research suggested that ubiquitination of TRIM25 substrates directly leads to the activation of the antiviral state [62].

Cyclic GMP-AMP synthase is an essential innate immune sensor with functions independent of the interferon response. For instance, cGAS exhibits non-catalytic roles in signaling to NF-κB and MAPK through STING. In addition, cGAS dimers can undergo LLPS through multimerization, forming biomolecular condensates to regulate cGAS activation [63,64]. In 2022, Zhao et al. discovered a new mechanism for DNA sensing, involving the formation of primary condensates between cGAS and G3BP1. In the presence of DNA, droplets formed by G3BP1-cGAS increase cGAMP synthesis, particularly when DNA levels are low, indicating that G3BP1 enhances the sensitivity threshold of cGAS to DNA [47]. Subsequently, Gantier et al. showed that the addition of DNA to the above G3BP1-cGAS condensates led to rapid displacement of G3BP1. Furthermore, zinc ions induce the primary condensation of cGAS in the absence of DNA, synergistically promoting LLPS in response to DNA in conjunction with G3BP1. This study suggests that the activation of DNA sensing depends on the formation of primary condensates between cGAS and G3BP1 [63]. SIRT2 is a unique regulatory factor within the cytoplasmic sirtuin family that negatively regulates the cGAS-STING signaling pathway. SIRT2, through interaction with G3BP1 and deacetylation, inhibits droplet formation as well as induces the disassembly of cGAS-G3BP1 condensates. This indicated that SIRT2 negatively regulates cGAS activation via G3BP1 deacetylation [65].

Oxidative stress can lead to increased levels of DNA damage, oxidation, and misfolded proteins [66]. In 2020, Somasekharan et al. indicated that oxidative stress alters the distribution of transcripts. Under arsenite exposure, transcripts associated with G3BP1 and polysome (PS) enrichment encoded proteins involved in different response pathways. G3BP1 guides transcript partitioning, enables mRNA translational reprogramming, and supports stress adaptation. In 2022, Singh et al. discovered that the transcriptional response to oxidative stress was independent of SG formation [67].

3. G3BP1 and SGs

1. SG formation

SGs are cytoplasmic biomolecular condensates in eukaryotic cells consisting of untranslated messenger ribonucleoprotein complexes (mRNPs) that aggregate during the translation initiation stage, leading to the formation of stalled RNAs and RBPs. SGs protect RNA from oxidative, osmotic, and heat shock stresses [68,69]. They are formed when RBPs interact with each other and aggregate into mRNPs, creating a substance resembling liquid droplets in response to environmental pressure. In addition to protein-protein interactions, the interactions of intrinsically disordered regions in proteins are also crucial for SG formation. When RNA and RBPs are dispersed in the cytoplasm or nucleoplasm and aggregate into condensed phases, SG particles assemble through LLPS, driven by homotypic interactions mediated by the intrinsically disordered regions of proteins [8,70]. This process is facilitated by the self-association of protein intrinsically disorder regions [71] (Fig. 2).

In 2020, Yang et al. discovered that the uneven distribution of interactions in the core protein-RNA interaction network can trigger LLPS, leading to SG formation. The central player in this interaction is G3BP1, and the RNA within this network promote LLPS. As an RBPs crucial for SG formation, G3BP1 initiates RNA-dependent LLPS in response to increased levels of free RNA in cells. In addition, the interactions between three distinct intrinsically disordered regions in G3BP1 regulate the intrinsic propensity for LLPS [8]. Filamin A (FLNA) is a mechanosensitive actin-crosslinking protein that interacts with various proteins to convert mechanical forces into biochemical signals by interacting with various proteins [72]. In 2023, Feng et al. showed that the force-dependent interactions between filamin A and G3BP1 modulate SG formation. Moreover, RNA interferes with the interaction between FLNA and G3BP1, thereby disrupting SG formation [73].

2. G3BP1 regulates SG assembly

2.1 Promoting assembly

G3BPs are essential components for the assembly of SGs under various stress conditions, and the absence of other SG components only affects the size or quantity of SGs [10,74]. Data from Guillén-Boixet et al. in 2020 suggested that SGs are not solely formed by interactions between G3BP molecules but also assemble through heterotypic phase separation mediated by G3BP1 and RNA [23]. Jumonji C (JmjC) domain-containing protein 6 (JMJD6), the first-described arginine demethylase [75], is a novel SG component that interacts directly with G3BP1. Studies have indicated that JMJD6 interacts with G3BP1, and its expression reduces G3BP1 monomethylation and asymmetric dimethylation at three arginine residues. JMJD6 acts directly or indirectly as an arginine demethylase for G3BP1, promoting the formation of SGs [76].

2.2 Inhibiting assembly

The African swine fever virus (ASFV) S273R protein (pS273R) is the only cysteine proteinase encoded by the ASFV genome. It interacts with G3BP1, affecting SG formation [77]. In 2023, Li et al. showed that pS273R cleaves G3BP1 into two fragments, thereby losing its ability to induce SG formation and antiviral activity. ASFV pS273R inhibits SG assembly by cleaving the nucleoprotein G3BP1, thus promoting viral replication [78]. In 2020, Lee et al. determined that the testis-specific protein, MAGE-B2, lowered G3BP protein levels below the critical concentration for LLPS and inhibited SG assembly. Specifically, MAGE-B2 suppresses SG assembly by inhibiting G3BP translation, thereby enhancing cellular stress tolerance [52]. In 2021, Samir et al. reported that TLR and IKK complex-mediated innate immune signaling also suppresses SG assembly [79].

2.3 Facilitating disassembly

Owing to the highly dynamic assembly of untranslated mRNA and proteins, SGs form through LLPS under cellular stress [80]. To investigate their disassembly, in 2023, Yang et al. screened six E3 ubiquitin ligases present in the SGs and identified tripartite motif-containing 21 (TRIM21) as the central regulatory factor in SG homeostasis. TRIM21 catalyzes the K63-linked ubiquitination of G3BP1, thereby inhibiting LLPS. In addition, under oxidative stress, endogenous SQSTM1 and CALCOCO2 localize to the periphery of SGs, mediating their disassembly [81]. SERPINE1 mRNA-binding protein 1 (SERBP1) is a common SG component and a conserved regulator for SG clearance in somatic cells and male reproductive cells [82]. In 2023, Wang et al. discovered that

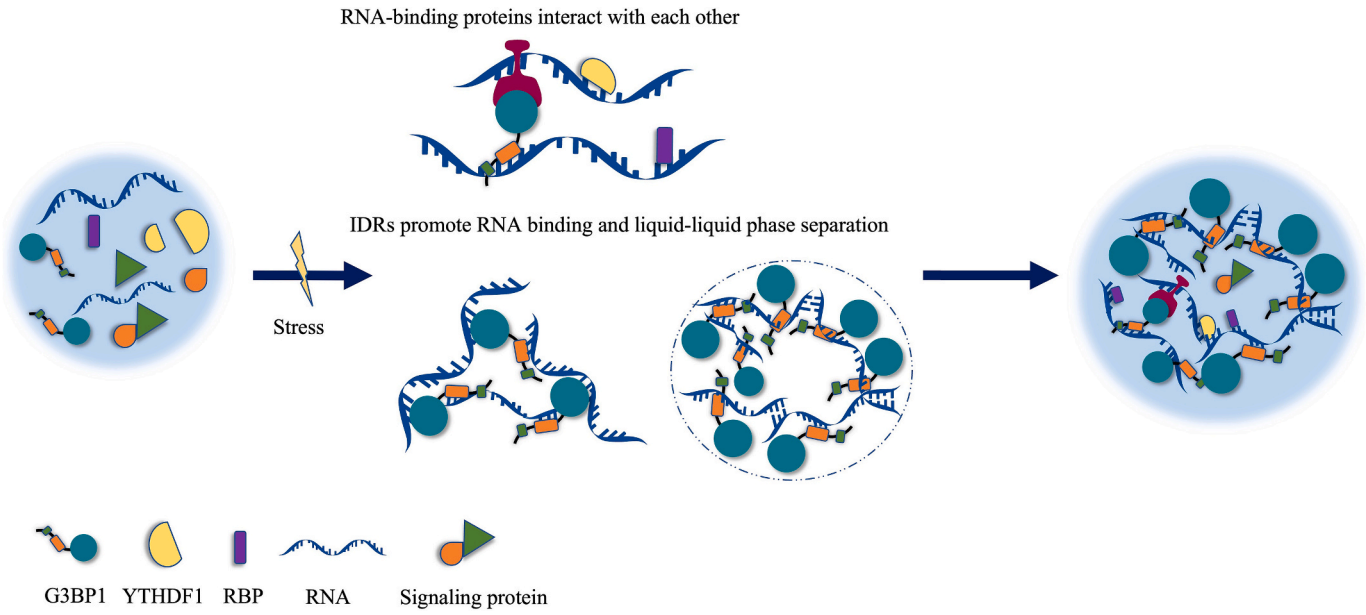

Fig. 2. SG formation mechanism. When eukaryotic cells are subjected to environmental stresses (such as oxidative, osmotic, or heat shock stress), interactions between RBPs centered on G3BP1 aggregate mRNPs to form droplet-like substances, in addition to IDRs promoting RNA binding and LLPS to form SGs.

SERBP1 promotes SG disassembly by regulating 26S proteasome activity and G3BP1 ubiquitination, thereby protecting male reproductive cells from heat stress damage [83].

4. G3BP1 and non-neoplastic diseases

1. Neurological system

Neurodegenerative diseases are characterized by loss of neurons and/or myelin sheaths, leading to progressive functional impairment over time. Common chronic neurodegenerative diseases include spinocerebellar ataxias (SCAs), Huntington's disease (HD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) [84]. In the nervous system, G3BP1 facilitates neural development and regulates neurodegenerative diseases through stress-induced membrane-less organelles referred to as SGs.

Polyglutamine diseases are a group of neurodegenerative disorders that affect the central nervous system and include HD, spinal muscular atrophy, dentatorubral-pallidoluysian atrophy, and various subtypes of SCAs. Polyglutamine diseases, such as SCAs, have commonalities, such as cerebellar dysfunction leading to ataxia. In a study conducted in 2023 by Koppenol et al., reduced levels of G3BP1 were detected in the cells of patients with SCA2 and SCA3, indicating impaired G3BP1 function in these diseases. Overexpression of G3BP1 delivered via lentiviral vectors to the cerebellum of transgenic mouse models of SCA3 and SCA1 reduced protein aggregation and contributed to the preservation of neuronal cells. Furthermore, in a transgenic mouse model of SCA1 with a severe ataxic phenotype, lentiviral delivery of G3BP1 to the cerebellum improved several motor deficits [85]. This suggests that G3BP1 plays a protective role against SCA progression. When SCA occurs, the protein levels of G3BP1 decrease, thereby exacerbating protein aggregation and promoting disease progression. Therefore, supplementation therapy targeting G3BP1 may be a future research direction for the treatment of SCA.

HD is a neurodegenerative disorder caused by mutations and amplification of the polyglutamine (polyQ) repeat sequence in huntingtin protein (HTT), leading to its aggregation [86]. In 2023, Gutiérrez-Garcia et al. discovered that enhanced levels of G3BP1 induced proteasomal degradation of mutant HTT and prevented its aggregation. However, the formation of SGs hinders these beneficial effects. The authors showed that under normal conditions, G3BP1 promotes HTT degradation. In addition, under stress conditions, G3BP1 accumulates within SGs, losing its ability to interact with mutant HTT, resulting in the persistence of polyQ-expanded HTT aggregates after stress relief [87]. Furthermore, chronic expression of mutant HTT in HD generates various forms of cellular stress, including the activation of the unfolded protein response and oxidative stress. In 2021, Sanchez et al. observed a significant increase in G3BP1 granules in mouse models of HD and in human brain tissues. In addition, a nuclear RNA/DNA-binding protein associated with SGs, TAR DNA-binding protein 43 (TDP-43), is mislocalized to the cytoplasm of G3BP1-positive HD cortical neurons. These findings suggest that dynamic changes in G3BP1 SGs may play a role in the pathophysiology of HD [88].

AD is a slowly progressing neurodegenerative disorder characterized by the formation of intraneuronal neurofibrillary tangles composed of tau aggregates, which is a significant pathological hallmark of AD [89]. Environmental and physiological stressors can accelerate the pathogenesis of AD. SGs, which contain translationally stalled mRNA, suggest that impaired RNA metabolism in neurons may affect AD progression, although the underlying mechanisms remain unclear. To address these questions, Sato et al. utilized eCLIP-seq technology to validate that G3BP1 and G3BP2 proteins could directly bind to numerous mRNAs and lncRNAs by 2023. During SG formation, RNA molecules, particularly mRNA and lncRNAs, are sequestered, leading to the accumulation of AD-related gene transcripts. This resulted in enhanced or reduced protein levels within the co-expressed modules of AD-related proteins. These findings indicate that SGs can directly modulate the development of AD and provide new possibilities for the treatment [90]. In 2022, Gao et al. determined that treating cells with zinc increased the interaction between full-length Tau and G3BP1 within SGs, promoting the formation of tau filaments and exacerbating tau toxicity in neuronal cells, thereby worsening AD [91].

ALS is primarily characterized by damage to the upper motor neurons in the motor cortex and the lower motor neurons in the spinal cord and brainstem, leading to gradual weakness and atrophy of the muscles in the limbs, trunk, chest, and abdomen. The non-receptor tyrosine kinase c-Abl plays a crucial role in the pathogenesis of several neurodegenerative diseases, including AD and Parkinson's disease (PD). TDP-43 is the primary protein component in ALS pathological deposits [92]. In 2022, Lee et al. identified TDP-43 as a novel c-Abl substrate. Phosphorylation of TDP-43 at tyrosine 43 by c-Abl increases the cytoplasmic

levels of TDP-43 as well as enhances the formation of G3BP1-positive SGs in human neuroblastoma cells (SH-SY5Y) [93]. In addition, TDP-43 has been identified as a major component of ubiquitin-positive cytoplasmic inclusions in sporadic and familial ALS residual motor neurons, and is a pathogenic gene in autosomal dominant inherited familial ALS. In 2021, research by Hadjara Sidibé et al. demonstrated that in ALS/frontotemporal dementia (FTD), depletion of TDP-43 in the nucleus resulted in compromised stability of G3BP1 mRNA. This causes impaired SG responses in affected neurons, contributing to the progression of the neurodegenerative proteinopathies ALS and FTD [37].

Repeat expansion of hexanucleotide (GGGGCC)n in C9orf72 can lead to ALS and FTD. This mechanism involves the generation of RNA foci, dipeptide repeat proteins, or toxicity resulting from the loss of C9orf72 protein. Nuclear-cytoplasmic transport (NCT) defects are considered to be the pathogenic mechanisms underlying the toxicity of repeat expansions. In 2023, McGoldrick et al. discovered that the depletion of C9orf72 disrupts Ran-GTPase gradients and nucleocytoplasmic transport, leading to the formation of diverse components of Importin β-1 granules, which exhibit co-immunoreactivity with G3BP1 and K63-ubiquitin [94]. In the same year, Sahana et al. showed that toxic dipeptide repeat sequences produced under ALS/FTD conditions activate c-Jun N-terminal kinase (JNK). The activation of JNK in the nucleus induces histone modifications, thereby increasing G3BP1 expression, promoting SG assembly, and contributing to neurodegeneration [95].

Under environmental stress, several mutations associated with Charcot-Marie-Tooth 2 (CMT2)-type neuropathy share similar characteristics when entering the SGs. In SGs, these mutated proteins exhibit abnormal interactions with G3BP1 and are integrated into the SG pathway. In 2023, Cui et al. showed that this process disrupts SG-mediated stress responses, thereby increasing the vulnerability of motor neurons to stress. Therefore, disrupting these abnormal interactions can rescue SG abnormalities and alleviate motor deficits in CMT2 mice [96]. NDDs constitute a group of common developmental brain dysfunction diseases, including intellectual disability, autism, attention deficit hyperactivity disorder (ADHD), communication disorders, motor disorders (such as cerebral palsy), and specific learning disorders [97]. Recent studies have revealed the crucial role of SGs in maintaining gene expression homeostasis during embryonic brain development [98,99].

Based on the aforementioned research, we determined that G3BP1 may play a protective role in neurodegenerative diseases and that increasing its protein levels may alleviate the symptoms of neurodegenerative diseases. However, when neurons respond to external stimuli by forming SGs centered around G3BP1, they may recruit key proteins, such as TDP-43 and Tau, leading to mislocalization or interaction errors. Furthermore, the increased abnormal assembly of SG and recruitment of mRNA and lncRNAs may contribute to the onset or exacerbation of neurodegenerative diseases. Therefore, inhibiting the abnormal assembly of SGs and promoting G3BP1 expression may represent promising therapeutic strategies for this condition.

2. Immune system

SGs play a crucial role in controlled activation of the retinoic acid-inducible gene I (RIG-I)-like receptor (RLR) signaling pathway. This receptor recognizes viral double-stranded RNA (dsRNA) and initiates an antiviral innate immune response, triggering systemic inflammation and immunopathology [100]. If G3BP1 is deficient, dsRNAs can induce excessive inflammation and immune-mediated cell apoptosis [23]. In 2023, a study by Paget et al. highlighted the role of SGs in maintaining cellular homeostasis by inhibiting toxic immune responses and viral replication [101].

Intracellular nucleic acid detection is a fundamental mechanism in host defense against infections, and dysregulation of nucleic acid sensing is the primary cause of multiple autoimmune diseases. G3BP1 plays a crucial role in immune responses induced by cellular DNA and RNA. In 2021, Cai et al. showed that in human and murine cells, G3BP1 deficiency inhibited DNA-induced cGAS activation and reduced the binding of RIG-I to RNA. Research suggests that the reduction of type I interferons induced by intracellular DNA and RNA through G3BP1 inhibition can be achieved using a natural compound discovered in grape skin, resveratrol (RSVL). Using an experimental mouse model of Aicardi-Goutières syndrome, an autoimmune disease that occurs in humans, the authors showed that RSVL effectively alleviated the autoimmune response triggered by intracellular nucleic acids. This study indicated a broader role for G3BP1 in sensing different types of intracellular nucleic acids [102].

3. Circulatory system

Coronary atherosclerotic heart disease (coronary heart disease) refers to the deposition of lipid substances in the normally smooth arterial intima owing to abnormal lipid metabolism [103]. This accumulation formed white plaques resembling a porridge on the arterial intima. As these plaques gradually increase in size, they narrow the arterial lumen, obstruct the blood flow, and cause myocardial ischemia, resulting in angina pectoris. Placement of coronary artery stents is a common method for treating coronary heart disease. In 2020, Xia et al. conducted a follow-up study involving 95 patients who underwent stent placement to investigate the effects of glycemic variability (GV) on intimal hyperplasia and plaque stability after coronary artery stent placement. Through optical coherence tomography; western blot analysis of Becn1, LC3B, p62, G3BP1, and NLRP3 protein levels in the intima; and in vitro experiments with THP-1 cells, it was determined that GV may affect intimal hyperplasia and plaque stability through autophagy-mediated G3BP1/NLRP3 inflammasome signaling, suggesting that glycemic variability and autophagy-mediated G3BP1/NLRP3 inflammasome signaling may be promising targets for the treatment of coronary heart disease [38].

SGs are membrane-less cellular organelles formed in response to cellular stress and play a crucial role in various cell signaling pathways. The role of SGs in sepsis-induced myocardial dysfunction has not been fully elucidated. In 2023, Wang et al. treated neonatal cardiomyocytes (CMs) with lipopolysaccharide (LPS), a component of bacterial cell walls. The results indicated that LPS stimulation in CMs triggered SG activation, leading to increased phosphorylation of eIF2α, elevated production of TNF-α, and reduced cellular response of cAMP to dobutamine. Pharmacological inhibition of SGs increased TNF-α expression in LPS-treated CMs and decreased intracellular cAMP levels. Overexpression of G3BP1 enhanced SG activation, attenuated LPS-induced increase in TNF-α expression, improved CM contractility, and prevented LPS-induced dissipation of mitochondrial membrane potential in CMs [104].

Recently, G3BP1 was identified as a crucial regulator of cardiac hypertrophy within the cardiovascular system. It plays an irreplaceable role in maintaining the maturity of myocardial cells and levels of microRNA-1 (miR-1). Stimulation of cardiac hypertrophy induces an increase in G3BP1, leading to a selective reduction in pre-miR-1, consequently lowering the levels of mature miR-1. In addition, downregulation of mature miR-1 requires inhibition of key transcriptional and translational targets, serving as a hallmark of cardiac hypertrophy [105]. In 2022, Alikunju et al. studied the role of G3BP1 in quiescent cardiomyocytes and in growth factor-induced hypertrophic cells. By downregulating endogenous G3BP1, the authors observed inhibition of genes involved in calcium handling, myocardial contraction, action potential, and myotube structure. G3BP1 knockdown also restricted endothelin-1 (ET-1)-induced cardiomyocyte hypertrophy. However, simultaneous silencing of both G3BP1 and miR-1 rescued the observed gene expression changes, and the knockdown of G3BP1 alone had an inhibitory effect on cardiomyocyte hypertrophy. Moreover, exogenous G3BP1 reversed the gene expression inhibition induced by miR-1. Therefore, we propose that G3BP1, by influencing the levels of mature miR-1, regulates crucial genes enriched in the heart and those involved in the development of myocardial cell hypertrophy [106].

4. Respiratory system

Respiratory diseases are closely associated with viruses including

influenza viruses, coronaviruses, and respiratory syncytial virus (RSV). Upon entering the human body, these viruses can cause respiratory infections characterized by symptoms, such as cough, runny nose, and sore throat [107,108]. Strong research focus is currently placed on the relationship between viruses and G3BP1 as well as SGs. This paragraph primarily discusses the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the coronavirus disease of 2019 (COVID-19), on G3BP1 and SG formation after invading the human body.

SARS-CoV-2, the pathogen responsible for the 2019 COVID-19 pandemic, has gained research attention in recent years owing to its strong transmissibility, long incubation period, and high pathogenicity. In 2023, Cai et al. discovered that SARS-CoV-2 infection led to the accumulation of mitochondrial DNA (mtDNA), activating the cGAS-mediated interferon-I (IFN-I) signaling pathway. In addition, the nucleocapsid protein (N) of SARS-CoV-2 restricts its cGAS DNA recognition capability, thereby impairing cGAS-induced IFN-I signal transduction. This mechanism involves disruption of cGAS and G3BP1 assembly by N protein-induced DNA-induced LLPS, thus impairing dsDNA detection by cGAS [109]. In the same year, Yang discovered that a mutation in the F17 region of the N protein can affect its interaction with G3BP1, suggesting that the G3BP1-N interaction inhibits SG formation, thereby promoting infection [110]. In 2022, Liu et al. showed that the N protein of SARS-CoV-2 effectively inhibited G3BP-mediated SG formation, overcoming G3BP1-mediated antiviral innate immunity to enhance viral infection [111]. Furthermore, Zheng et al. determined that the interaction between the N protein and G3BP1 can prevent the formation of antiviral SGs and inhibit the activation of RIG-I by the cofactors G3BP1 and PACT [112].

To gain a better understanding of the inhibitory effects of coronaviruses on SGs, Dolliver et al. conducted an analysis in 2022 comparing human coronavirus OC43 (HCoV-OC43) infection, which causes the common cold, with SG formation during the SARS-CoV-2 pandemic. In their experiments, the authors did not observe SGs in infected cells, indicating that both viruses suppress the phosphorylation of eIF2α and the formation of SGs induced by extracellular stress. In addition, a significant decrease in the levels of the SG-nucleating protein, G3BP1, was observed in cells infected with SARS-CoV-2. The experimental results indicated that G3BP1 possesses antiviral activity and that there are multiple mechanisms of SG inhibition between HCoV-OC43 and SARS-CoV-2. The formation of SGs may represent an essential antiviral host defense mechanism adopted by coronaviruses to ensure efficient replication [113]. Host-targeted antiviral therapy is a promising therapeutic option for COVID-19 and its emerging variants. In 2023, Merino et al. showed that the nucleolar protein nucleolin (NCL) interacts with SARS-CoV-2 viral proteins and co-localizes with the N protein in the nucleolus and SGs. NCL knockdown reduces G3BP1 levels and viral replication, thereby enhancing the survival of infected host cells [114]. In 2022, Kim et al. discovered that the impact of SARS-CoV-2 infection on SG formation varied depending on the host cell type rather than the virus strain [115]. In 2023, LeBlanc et al. showed that the SARS-CoV-2 N protein could counteract two key antiviral pathways activated by dsRNA, namely PKR and OAS/RNase L. Therefore, the ability of the SARS-CoV-2 N protein to inhibit innate antiviral activity may be a crucial factor contributing to virus transmissibility and pathogenicity [116].

Crystal structure analysis of the complex between the NTF2-like domain of G3BP1 ($G3BP1_{NTF2}$) and the N protein derived from SARS-CoV-2 (residues 1–25, $N_{1–25}$) reveals that SARS-CoV-2 $N_{1–25}$ occupies the conserved surface groove of G3BP1NTF2 through surface complementarity. In 2022, Biswal et al. showed that the φ-x-F (φ, hydrophobic residue) motif constitutes the primary determinant cluster for $G3BP1_{NTF2}$ targeting proteins, with the side-chain sequence supporting various secondary interactions. This study demonstrated that mutations in key interacting residues of the SARS-CoV-2 $N_{1–25}$- $G3BP1_{NTF2}$ complex disrupt in vitro interactions between SARS-CoV-2 N and G3BP1 [117]. In 2021, Ali et al. identified imatinib and dasatinib as potential regulators of the G3BP1/2 gene and its regulatory factors, suggesting them as candidate drugs for COVID-19 relief and as antiviral agents targeting the N and G3BP1/2 proteins [118]. This review summarizes the relationship between G3BP1 and non-tumor diseases (Table 1).

Based on the above results, we determined that G3BP1, as well as SG formation with G3BP1 as the core, may represent crucial antiviral mechanisms. Therefore, promoting G3BP1 expression, inhibiting the interaction between G3BP1 and the N protein (or other key proteins affecting SG formation), facilitating SG formation, may be pivotal measures for treating COVID-19 in the future.

5. Reproductive system

In 2023, Li et al. established an in vivo model of fluoro-chloropyridine-chloroacetamide-induced (FCPA) induced testicular and germ cell toxicity. They investigated the role and mechanism of the G3BP1 gene-mediated P38 MAPK/JNK pathway in FCPA-induced testicular and germ cell damage. These findings indicate that rats exposed to FCPA experience testicular and sperm cell damage, potentially leading to changes in pathological morphology and androgen levels. In addition, the antioxidant capacity decreased. When intracellular antioxidant capacity is compromised, the expression and activity of G3BP1 are inhibited. This inhibition, in turn, activates the P38 MAPK/JNK and intracellular apoptotic pathways, leading to apoptosis of reproductive cells [39].

5. Role of G3BP1 in tumors

1. Digestive system

Oral squamous cell carcinoma (OSCC) is a malignant tumor that originates from squamous epithelial cells in the oral cavity. G3BP1 is an oncogene that plays crucial roles in OSCC development. Current research indicates that the mRNA levels of G3BP1 in OSCC are significantly higher than those in normal tissues, and elevated G3BP1 mRNA levels may reduce overall patient survival rates [119]. In 2021, Hu et al. showed that in OSCC tissues, G3BP1 protein levels were significantly upregulated and positively correlated with Ki67 but negatively correlated with Cleaved-caspase3 [120]. In 2022, Liu et al. discovered that G3BP1 was highly expressed in M2 macrophages (tumor-associated macrophages, TAMs), and under stress conditions, SG formation in M2 TAMs enhances the expression of CCL13, promoting OSCC metastasis in vitro and in vivo. The authors also analyzed the protein expression profile of M2-type monocyte-derived macrophages (MDMs-M2) using mass spectrometry, revealing a high expression of G3BP1 in MDMs-M2. Furthermore, SG formation improved the stability of DDX3Y/hnRNPF-mediated CCL13 mRNA, enhancing CCL13 expression and promoted OSCC metastasis [121]. Quercetin significantly inhibited glycolysis and cell proliferation in OSCC; however, its mechanism of action remains unclear. In 2023, Hu et al. showed that quercetin inhibited G3BP1/YWHAZ signaling in a dose-dependent manner, and this effect was antagonized when G3BP1 was overexpressed. Therefore, quercetin inhibits glycolysis and cell proliferation in OSCC by suppressing the G3BP1/YWHAZ axis [122].

Colorectal cancer (CRC) is a common malignant tumor of the gastrointestinal tract, with incidence and mortality ranking only below those of gastric (GC), esophageal, and primary liver cancers among malignant tumors of the digestive system. In 2020, Li et al. determined that overexpression of G3BP1 activates the β-catenin signaling pathway, thereby promoting the progression of colon cancer [123]. In the same year, Cui et al. reported that patients with CRC with higher expression of homer scaffolding protein 1 (Homer1) had lower survival rates. Homer1 upregulated G3BP1 in vitro, thereby promoting the proliferation, migration, and invasion of CRC cells [124]. In 2022, Li et al. discovered that LINC01088 was significantly upregulated in CRC tissues and CRC cell lines compared to adjacent normal tissues and colonic epithelial cells. LINC01088, by binding to miR-548b-5p and miR-548c-5p, promotes the expression of G3BP1 and programmed death ligand 1 (PD-L1),

Table 1
G3BP1 and non-neoplastic diseases in this review.

G3BP1 and non-neoplastic diseases			
System	Disease	Role of G3BP1 in disease	References
Nervous system	Spinocerebellar ataxias	G3BP1 overexpression not only reduces protein aggregation but also helps protect nerve cells.	PMID:36511898
	Huntington's disease	TDP-43 is mislocalised to the cytoplasm of G3BP1 granule-positive HD cortical neurons	PMID:33945510
	Alzheimer's disease	G3BP1 and G3BP2 proteins bind directly to a large number of mRNAs and lncRNAs, sequestering them when externally stimulated, leading to the accumulation of transcripts of AD-related genes	PMID:37219408
		Zinc treatment would not only increase the interaction between full-length Tau and G3BP1 within stress granules, but also increase the toxicity of Tau in neuronal cells thereby worsening AD.	PMID:35405154
	Amyotrophic lateral sclerosis	TDP-43 nuclear depletion causes impaired G3BP1 mRNA stability and an impaired stress granule response that promotes ALS.	PMID:34115105
	Frontotemporal dementia	Activated JNK induces histone modifications that increase G3BP1 expression and promote stress granule assembly and neurodegeneration.	PMID:37015810
	Charcot-Marie-Tooth 2	CMT2 mutant protein interacts abnormally with G3BP1 and integrates into the SG pathway, disrupting the stress response mediated by SG and increasing the stress vulnerability of motor neurons.	PMID:36738734
Circulatory system	Coronary heart disease	GV may influence endothelial proliferation and plaque stability through autophagy-mediated G3BP1/NLRP3 inflammatory vesicle signaling	PMID:33313133
	Myocardial dysfunction induced by sepsis	Overexpression of G3BP1 increased SG activation and improved contractility of CMs, and in addition SG prevented LPS-induced mitochondrial membrane potential dissipation in CM.	PMID:37312024
	Myocardial hypertrophy	G3BP1 regulates important cardiac enrichment genes and genes involved in the development of cardiomyocyte hypertrophy by affecting mature miR-1 levels.	PMID:35017014
respiratory system	COVID-19	N protein disrupts cGAS assembly with G3BP1 by DNA-induced liquid-liquid phase separation (LLPS)	PMID:37100798
		Mutation of F17 in the N protein affects its interaction with G3BP1	PMID: 37425880
		N protein effectively inhibits G3BP-mediated SG formation and enhances viral infection by overcoming G3BP1-mediated antiviral innate immunity	PMID: 35652658
		N protein interacts with G3BP1 and prevents the formation of antiviral SGs	PMID:35075101
		The formation of SGs may represent an essential antiviral host defense mechanism adopted by coronaviruses to ensure efficient replication.	PMID:36534661
		Knockdown of NCL reduces G3BP1 and viral replication and improves survival of infected host cells.	PMID:36740097
		Mutations in key interacting residues of the SARS-CoV-2N1-25- G3BP1NTF2 complex disrupt SARS-CoV-2 N - G3BP1 interactions in vitro.	PMID:35240128

leading to phenotypic changes in CRC cells. Moreover, the knockout of LINC01088 downregulates PD-L1 expression, whereas the overexpression of G3BP1 restores PD-L1 expression [125].

GC is a malignant tumor originating in the epithelium of the gastric mucosa. G3BP1, as an assembly factor for SGs, has been reported to be overexpressed in GC [126]. In 2021, Zhao et al. showed that knocking out G3BP1 significantly increased the sensitivity of GC cells to chemotherapeutic drugs and that apoptosis and pro-apoptotic molecules were markedly elevated after G3BP1 knockout [127]. In 2023, Liu et al. discovered that the independent prognostic factor circIPO7 in patients with GC was downregulated in GC tissues and cells compared to that in adjacent tissues and normal epithelial cells. Moreover, overexpression of the circIPO7 complex blocks the interaction between caprin-1 and G3BP1, causing the separation of caprin-1 and its target mRNA from the ribosome, thereby inhibiting translation and inactivating the PI3K/AKT/mTOR pathway [128]. Bioinformatics studies have revealed the overexpression of the RBPs hexokinase domain component 1 (HKDC1) in GC. In 2023, Zhao et al. confirmed that the cancer protein kinase DNA-activated catalytic subunit (PRKDC) was a crucial downstream effector of HKDC1 in lipid metabolism-dependent GC development. G3BP1 can directly bind to HKDC1 and protect PRKDC mRNA from degradation, thereby accumulating PRKDC and enhancing the stability of PRKDC transcripts [129].

Hepatocellular carcinoma (HCC) is a malignant liver tumor that can be classified into primary and secondary categories. NOP2/Sun domain family member 2 (NSUN2) is an RNA methyltransferase responsible for the m5C modification of various RNAs. In 2023, Sun et al. showed that the oncogenic lncRNA H19 was a target of NSUN2, and 5-methylcytosine (m5C) modification enhanced the stability of H19 lncRNA, enabling it to specifically bind to G3BP1. This suggests that m5C-modified H19 lncRNAs promote the occurrence and development of tumors by interacting with G3BP1 [130].

Cholangiocarcinoma (CCA) is a malignant tumor arising from the extrahepatic bile ducts, including the bile ducts from the hepatic hilum to the lower end of the common bile duct, and is characterized by invasive growth and early lymphatic metastasis [126]. In 2023, Jiang et al. discovered that KIF14 was upregulated in CCA samples, especially in those with lymph node metastasis and vascular invasion. Subsequent mechanistic studies revealed that KIF14 interacts with the G3BP1/YBX1 complex, leading to enhanced activity of the NF-κB promoter and activation of the NF-κB pathway. Therefore, KIF14 is a potential oncogene

that aids in the prognostic assessment of patients with CCA [131].

2. Reproductive system

Breast cancer (BC) is characterized by the uncontrolled proliferation of breast epithelial cells under the influence of various carcinogenic factors. Y-box binding protein-1 (YB-1), a member of the DNA/RBP family, contains a conserved cold shock domain (CSD). YB-1 can promote the formation of stress-induced SGs in pancreatic and colon cells [132] and participates in the translational activation of G3BP1 mRNA [51]. In 2022, Lefort et al. showed increased expression of HIF1α (YB-1 translational target) and G3BP1 (element of stress-adaptive program), reflecting the levels of YB-1 in transformed BC cells [33]. In the same year, Liu et al. discovered an elevated expression of G3BP1 in BC, and knocking out G3BP1 reduced the proliferation and metastasis of BC cells. Membrane transport and phosphorylation of PKCζ were significantly inhibited after G3BP1 knockout, indicating that G3BP1 regulates the activation of PKCζ, thereby modulating the proliferation and metastasis of BC cells [133]. In 2021, Zhang et al. reported that increased G3BP1 interacting with GSK-3β leads to the inactivation of GSK-3β, inhibiting the phosphorylation and degradation of β-catenin. Disrupting their interaction accelerates the degradation of β-catenin, impairing the proliferative capacity of BC cells [32]. Small nucleolar noncoding RNAs (snoRNAs), conservative 60–300 nucleotide noncoding RNAs, participate in the post-transcriptional regulation of mRNA and noncoding RNA. In 2022, Hu et al. showed that G3BP1 loss inhibited the SNORA71A-mediated upregulation of ROCK2. In vivo, overexpression of SNORA71A promoted the growth of BC, whereas SNORA71A knockout inhibited the growth and metastasis of BC. The authors suggested that SNORA71A promotes BC metastasis by binding to G3BP1 and stabilizing ROCK2 [134]. In various BC cell lines, SETβ is the primary isoform of the tumor protein SET and is closely related to cellular stress responses. In 2023, Zhao et al. determined that SETβ inhibits the activation of stress-induced p38 MAPK signaling pathway and hinders the formation of G3BP1 and RNA complexes, thereby suppressing SG assembly. This suggests that SET is an important regulatory factor that dynamically controls the SG signaling pathway [31].

In addition to BC, G3BP1 also mediates the proliferation and metastasis of ovarian cancer (OC) in the female reproductive system. To explore its biological mechanisms, in 2021, Wang et al. discovered that extracellular vesicles (EVs) secreted by OC can enter recipient mesothelial cells. SPOCD1-AS within EVs induces mesothelial-to-mesenchymal transition (MMT) in recipient cells by interacting with G3BP1, promoting in vitro and in vivo peritoneal implantation. Furthermore, a G3BP1 interfering peptide based on F380/F382 residues blocked the interaction between SPOCD1-AS and G3BP1, inhibiting the MMT phenotype in mesothelial cells and reducing peritoneal metastasis in vivo [135]. In 2022, Li et al. showed that the loss of G3BP1 inhibited the proliferation, migration, and invasion of OC cells. Interaction between G3BP1 and ubiquitin-specific protease 10 (USP10) promotes tumor development. In addition, USP10 knockdown restored the G3BP1-induced proliferation, migration, and invasion of OC cells. These results suggest that the coordinated action of G3BP1 and USP10 promotes OC cell progression. Therefore, G3BP1 may serve as a novel therapeutic target in OC [136].

Prostate cancer (PCa) is a malignant tumor that arises from the epithelial cells of the prostate. SPOP is an E3 ubiquitin ligase and prostate-specific tumor suppressor with several key substrates having oncogenic functions. In 2021, Mukhopadhyay et al. discovered that G3BP1 interacts with SPOP and acts as a competitive inhibitor of Cul3SPOP. This study indicates that the G3BP1-SPOP ubiquitin signaling axis promotes PCa progression by activating the androgen receptor (AR) signaling. Therefore, patients with PCa with high levels of G3BP1 may be more responsive to AR-targeted therapies [137]. In 2021, Kumar et al. reported that the prolonged use of withaferin A (WA) upregulated the expression of proteins involved in stress response pathways. Our experiments showed that treatment of PCa cells with WA increased oxidative stress, promoted SG formation, reduced mRNA translation, and enhanced G3BP1 expression. The G3BP1 knockout prevents SG formation and increases the effectiveness of WA in reducing PCa cell viability [138]. In 2023, Campbell et al. reported that the cytoplasmic high-mobility group A2 (HMGA2) protein interacts with G3BP1. Endogenous knockdown of either HMGA2 or G3BP1 in PC3 cells reduces cell proliferation [139].

3. Other systems

G3BP1 is primarily associated with lung cancer of the respiratory system Studies have shown that the downregulation of G3BP1 in human lung cancer cells can inhibit the activation of focal adhesion kinase (FAK) and ERK1/2, thereby reducing the expression of NF-B. G3BP1 also suppresses the expression of matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), and urokinase-type plasminogen activator (uPA), thereby inhibiting the proliferation, invasion, and migration of lung cancer cells [140].

Neuroblastoma is the most common extracranial tumor in children. In 2023, Yang et al. determined that TRIM25, a member of the tripartite motif (TRIM) protein family, interacted with G3BP1. Further research revealed that reducing G3BP1 or knocking out TRIM25 can both inhibit the proliferation and migration of human neuroblastoma cells (SHSY5Y). In addition, TRIM25 promotes the proliferation and migration of SHSY5Y in a G3BP1-dependent manner [141]. Table 2 summarizes the relationship between G3BP1 and tumors in this review.

4. The role of G3BP1 in chemotherapy drugs

5. Role of G3BP1 in Chemotherapy Drugs

The use of chemotherapeutic drugs is one of the primary approaches to cancer treatment. Recently, researchers have discovered that chemotherapeutic drugs induce SG formation. In 2020, Zhan et al. conducted a comprehensive study and showed that platinum induces reactive oxygen species and stimulates SG assembly. In addition, the protein PKR can be activated by 5-fluorouracil (5-FU), leading to eIF2α phosphorylation and apoptosis. Arsenic trioxide, paclitaxel, and bortezomib can induce eIF2α phosphorylation by activating PKR, PERK, and HRI [142], respectively.

In summary, in most tumor diseases, the protein levels of G3BP1 are elevated compared to normal tissues, and it may interact with key pathway proteins (such as YWHAZ, β-catenin, SPOP, and ERK1/2) to alter downstream signaling. G3BP1 can also worsen disease progression by interacting with proteins related to tumor proliferation, migration, invasion (such as GSK-3β, SNORA71A, USP10, and FAK), or affecting lncRNA, thereby reducing overall patient survival rates. However, whether the regulatory role of G3BP1 in tumors depends on SG functions requires further investigation at the basic biological level. Future studies should focus on mutating key regions of G3BP1 involved in SG formation (such as the NTF2, RBD, or IDR domains) or altering the LLPS environment (such as by modulating pH and ATP concentrations [143,144]) to inhibit SG formation and explore the functional role of G3BP1.

6. Relationship between G3BP1 and viruses

G3BP1 is a multifunctional RBP involved in SG nucleation, and has been identified as an essential cofactor for alphaviruses. Alphaviruses belong to the Togaviridae family and their non-structural protein 3 (nsP3) contains an intrinsically disordered C-terminal hypervariable domain (HVD) that interacts with various host proteins associated with SGs. Alphaviruses include the Mayaro virus (MAYV) and Chikungunya viruses (CHIKV) [145]. MAYV is an arthritogenic alphavirus that causes local joint inflammation, and is prevalent in Amazonian countries. In 2021, Nowee et al. reported that MAYV growth in human cells required G3BP1, and G3BP1 which interact with nsP3. In infected cells, G3BP1 was recruited to membrane foci containing nsP3 and active replication complexes (Fig. 3A). Deletion of a single FGxF motif in MAYV nsP3 did not eliminate these phenotypes [146].

CHIKV is an RNA virus transmitted by mosquitoes that causes joint and muscle pains. In 2021, Lu et al. discovered that CHIKV nsP3 could displace G3BP1 from SG and disrupt SG formation [147]. In the same

Table 2
G3BP1 and tumors in this review.

G3BP1 and tumors			
Systems	Tumors	Role of G3BP1 in tumors	PMID
Digestive system	Oral squamous cell carcinoma	In oral squamous cell carcinoma tissues, G3BP1 protein levels were significantly up-regulated and positively correlated with Ki67, and negatively correlated with Cleaved-caspase3	PMID: 33987877
		G3BP1 was highly expressed in MDMs-M2 and SG formation enhanced CCL13 expression and promoted OSCC metastasis.	PMID: 36291863
		Quercetin inhibits glycolysis and cell proliferation in OSCC via the G3BP1/YWHAZ axis.	PMID: 35945655
	Colorectal cancer	Activation of β-catenin signaling upon G3BP1 overexpression promotes colon cancer progression.	PMID: 33000280
		Homer1 upregulates G3BP1 in vitro and promotes colorectal cancer cell proliferation, migration and invasion.	PMID: 32425603
		Binding of LINC01088 to miR-548b-5p and miR-548c-5p promotes the expression of G3BP1 and PD-L1, resulting in phenotypic changes in CRC cells	PMID: 35357586
	Gastric cancer	Knockdown of G3BP1 significantly increased the sensitivity of gastric cancer cells to chemotherapeutic agents.	PMID: 32989225
		Apoptosis and pro-apoptosis related molecules were significantly elevated after G3BP1 was knocked down.	
		Overexpression of the circIPO7 complex blocks the interaction between caprin-1 and G3BP1 and affects the PI3K/AKT/mTOR pathway.	PMID: 36732659
		G3BP1 directly binds to HKDC1 and protects PRKDC mRNA from degradation, thereby enhancing the stability of PRKDC transcripts.	PMID: 37423558
	Hepatocellular carcinoma	m5C-modified H19 lncRNA may promote hepatocarcinogenesis by binding to G3BP1	PMID: 32978516
	Colangio carcinoma	KIF14 binds and interacts with the G3BP1/YBX1 complex, leading to enhanced NF-κB promoter activity and activation of the NF-κB pathway.	PMID: 36922675
Reproductive system	Breast cancer	G3BP1 expression is elevated in breast cancer, and knockdown of G3BP1 reduces breast cancer cell proliferation and metastasis.	PMID: 36330442
		Elevated G3BP1 interacts with GSK-3β to inactivate GSK-3β and inhibit the phosphorylation and degradation of β-catenin, thereby impairing the proliferation of breast cancer cells.	PMID: 33536604
		SNORA71A promotes breast cancer metastasis by binding to G3BP1 and stabilizing ROCK2	PMID: 35100495
		SETβ prevents G3BP1 and RNA complex formation thereby inhibiting SG assembly.	PMID: 36534342
	Ovarian cancer	SPOCD1-AS interaction with G3BP1 induces MMT process in mesothelial cells.	PMID: 33726799
		G3BP1 interfering peptide based on residues F380/F382 also blocks SPOCD1-AS/G3BP1 interaction and inhibits the MMT phenotype of mesothelial cells.	
		G3BP1 synergises with USP10 to promote OC cell progression	PMID: 34967276
	Prostate cancer	G3BP1-SPOP ubiquitin signaling axis promotes PCa progression by activating AR signaling.	PMID: 34795264
		WA treatment of PCa cells increased oxidative stress, promoted SG formation, decreased mRNA translation and increased G3BP1 expression.	PMID: 34298187
		Knockdown of G3BP1 prevented SG formation and enhanced WA to decrease PCa cell survival.	
		Endogenous knockdown of HMGA2 or G3BP1 reduces cell proliferation.	PMID: 37113783
Respiratory system	Lung cancer	The down regulation of G3BP1 can not only inhibit the activation of FAK andERK1/2, reduce the expression of NF-B, but also reduce the expression levels of MMP- 2, MMP-9 and uPA, thus inhibiting the proliferation, invasion and migration of lung cancer cells.	PMID: 24157923
Nervous system	Neuroblastoma	Reducing G3BP1 or knocking down TRIM25 inhibited SHSY5Y proliferation and migration, and TRIM25 promoted SHSY5Y proliferation and migration in a G3BP1-dependent manner.	PMID: 37302696

year, Teppor et al. demonstrated that nsP3 in CHIKV is phosphorylated and that eliminating all phosphorylation sites in nsP3 can completely block CHIKV replicase activity. Thus, the phosphorylation of nsP3 and phosphorylation sites in nsP3 represent targets for antiviral compounds and the attenuation of CHIKV [148]. In 2023, Yin et al. showed that the HVD of the CHIKV nsP3 protein interacts with G3BP1, which is a necessary condition for CHIKV replication [149] (Fig. 3A).

Viruses of the family Flaviviridae, including Yellow Fever Virus (YFV) and Hepatitis C Virus (HCV), primarily infect mammals. They possess single-stranded RNA as their genetic material, and the viral particles have an envelope with a diameter of 40–60 nm. The YFV is an RNA virus that predominantly targets the liver. In 2020, Beauclair et al. discovered that YFV infection promotes SG formation in a PKR-dependent manner. Interestingly, the formation of pro-inflammatory mediators after YFV infection does not require SG involvement [149,150] (Fig. 3B). LINE-1 (L1) retrotransposons are autonomous

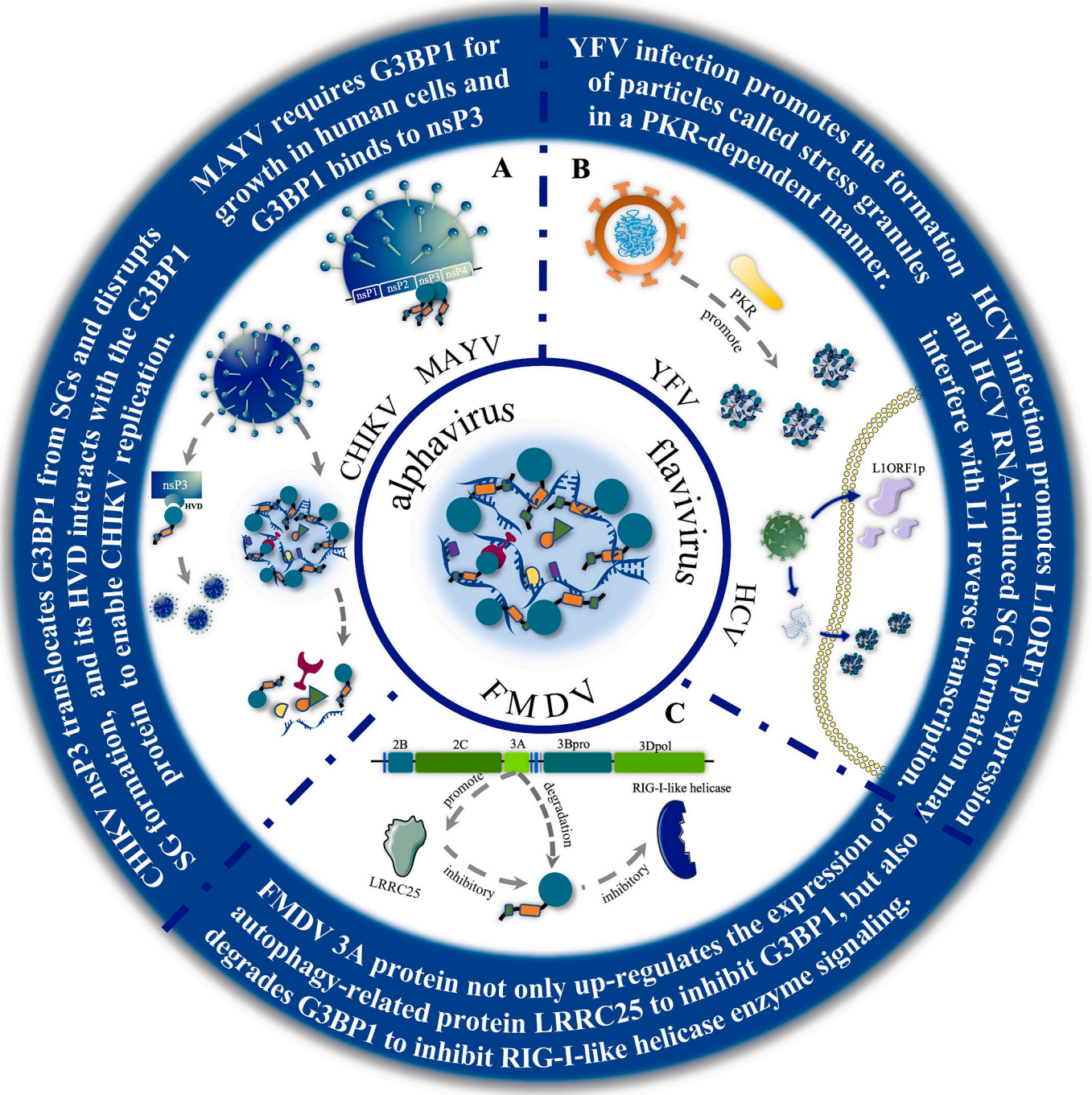

Fig. 3. Role of G3BP1 in viruses. A: Role of G3BP1 in alphaviruses MAYV and CHIKV
B: Relationship of G3BP1-centred SG with YFV and HCV of the family Flaviviridae
C: Effect of FMDV on G3BP1c.

transposable elements affecting gene expression and genomic integrity. In 2021, Schöbel et al. showed that HCV infection led to a significant increase in the levels of the endogenous L1-encoded ORF1 protein (L1ORF1p). In addition, HCV replication interfered with L1 retrotransposition, which is associated with HCV RNA-induced SG formation (Fig. 3B). This phenomenon can be improved by knocking out G3BP1 [151].

Foot-and-mouth disease (FMD) is caused by the foot-and-mouth disease virus (FMDV) and is an acute, febrile, and highly contagious infectious disease affecting cloven-hoofed animals such as cattle, sheep, and pigs. In 2020, Yang et al. reported that FMDV 3A protein inhibits the RIG-I-like helicase signaling pathway by degrading G3BP1. In addition, FMDV 3A suppresses G3BP1 by upregulating the expression of autophagy-related protein LRRC25. Similar effects were observed in other picornaviruses such as Seneca Valley virus (SVV) 3A and enterovirus 71 (EV71) 3A, which also degrade G3BP1 by upregulating LRRC25 expression [152] (Fig. 3C). SVV is an oncolytic RNA virus belonging to the family Picornaviridae. In 2020, Wei et al. showed that down-regulation of G3BP1 or expression of a non-phosphorylatable mutant of eIF2α inhibits SG formation but does not significantly impact SVV propagation. Furthermore, with the reduction of G3BP1, activation of the NF-κB signaling pathway decreases. In addition, SVV inhibited SG

formation during the late stages of infection [153].

Poliovirus (PV) is a typical single-stranded RNA virus with a functional mRNA genome primarily comprising three serotypes: 1, 2, and 3. However, the mechanisms underlying the interaction between this virus and the human body remain unclear [154]. Dougherty et al. determined that PV infection induces SG formation in the early stages of infection, followed by the inhibition of SG formation and dispersion of processing bodies (PBs) in the middle stage of infection. SG loss in the later stages of infection is attributed to the cleavage of G3BP1 by viral 3C proteinase (3Cpro), thereby inhibiting SG formation in cells. The authors observed continuous SGs throughout the infection process when expressing an uncleavable form of G3BP in PV-infected cells. However, the dispersion of PBs is not significantly related to the cleavage of specific factors by viral proteases, indicating the involvement of other viral proteins in inhibiting SG or PB formation [155–157].

7. Conclusion

In summary, G3BP1 is a multifunctional binding protein that serves as a key component in SG formation and acts as a crucial switch that triggers LLPS. In addition, G3BP1 is involved in RNA metabolism and signaling pathways, such as Ras, and influences the cell cycle, thereby regulating various diseases. SGs, a special type of membraneless organelles, have gained attention for their ability to temporarily halt the translation of non-essential proteins or stall untranslated mRNA when cells experience external stimuli. This mechanism plays a crucial role in the cellular responses to environmental stress. After external stimuli are removed, SGs are degraded, allowing suspended biological processes to resume, and cellular functions to return to normal.

The mechanism through which G3BP1 regulates various tumor and non-tumor diseases is currently a popular research topic. Among non-tumor diseases, neurological studies have been particularly extensive, suggesting that G3BP1 plays a role in neuronal development and maintenance. It also plays an important role in maintaining myocardial cell maturity and miR-1 levels. However, the role of G3BP1 in non-tumor diseases such as myocardial hypertrophy, atrial fibrillation, hepatitis, and Bartter's syndrome remains unclear and requires further exploration. In studies on viral infections that cause localized arthritis, hepatitis C, and hand-foot-mouth disease, G3BP1 was shown to interact with viral proteins to regulate SG assembly, thereby inhibiting viral RNA replication and exerting antiviral effects. However, G3BP1 may also act as a cofactor to promote viral replication, making the interaction between G3BP1 and the pathogen complex. Clarifying the mechanism may be useful in a new era of antiviral treatment.

Numerous studies have reported the role of G3BP1 in tumors. Studies have indicated that G3BP1 promotes tumor cell proliferation and migration and inhibits apoptosis by regulating signaling pathways such as Ras and PI3K/AKT. In cancer, G3BP1 acts as a pro-cancer factor that enhances cell proliferation, invasion, and metastasis. Compared to normal tissues, G3BP1 is expressed at higher levels in tumor tissues, suggesting its potential as a new indicator for cancer diagnosis, treatment, and prognosis. However, the current understanding of the regulatory mechanisms of G3BP1 in cancer is limited, and it is still unclear whether targeting G3BP1 and SGs can effectively inhibit tumors.

Abbreviations

LLPS	liquid-liquid phase separation
RBP	RNA-binding protein
LCD	low-complexity domains
SG	Stress Granule
G3BP1	Ras-GTPase-activating protein binding protein 1
NTF2	nuclear transport factor 2
IDR	intrinsically disordered region
RBD	RNA-binding domain
RRM	RNA recognition motif
RGG	arginine -glycine-rich
rasGAP	Ras- GTPase-activating protein
PKR	protein kinase R
eIF2α	eukaryotic initiation factor 2α
cGAS	Cyclic GMP-AMP synthase
3'UTR	3′-untranslated region
rG4s	RNA guanine quadruplexes
BTK	Bruton's tyrosine kinase
lncRNA	Long non-coding RNA
CALA	cytoplasmic G3BP1-associated lncRNA
UBAP2L	ubiquitin-associated protein 2-like
snoRNA	small nucleolar RNAs
YB-1	Y-box binding protein 1
PRMT8	protein arginine methyltransferase 8
TDRD3	Tudor Domain Containing 3
SASP	senescent-associated secretory phenotype
STAT3	Signal transducer and activator of transcription 3
TSC	tuberous sclerosis complex
mTORC1	mechanistic target of rapamycin complex 1
IFN	interferon
ISG	interferon- stimulated gene
NF90	Nuclear factor 90
TIA-1	T-cell intracytoplasmic antigen
TRIM	tripartite motif
PS	polysomes
mRNPs	messenger ribonucleoprotein complexes
FLNA	Filamin A
JMJD6	Jumonji C (JmjC) domain-containing protein 6
ASFV	African swine fever virus
SCAs	spinocerebellar ataxias
HD	Huntington's disease
AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
HTT	huntingtin protein
polyQ	polyglutamine
TDP-43	TAR DNA-binding protein 43
FTD	frontotemporal dementia
NCT	nucleocytoplasmic transport
NDD	neurodevelopmental disorder
RIG-I	retinoic acid inducible gene I
RSVL	resveratrol
GV	glycaemic variability
LPS	lipopolysaccharide
CMs	cardiomyocytes
miR-1	microRNA-1
OSCC	oral squamous cell carcinoma
TAMs	tumor-associated macrophages
MDMs-M2	M2 type monocyte-derived macrophages
CRC	colorectal cancer
Homer1	Homer scaffolding protein 1
PD-L1	programmed death ligand 1
GC	gastric cancer
HKDC1	RNA-binding protein hexokinase domain component 1
HCC	hepatocellular carcinoma
NSUN2	NOP2/Sun domain family member 2
m5C	5-methylcytosine
CCA	colangio carcinoma
CSD	cold-shock domain
SET	SE translocation
OC	ovarian cancer
EVs	extracellular vesicles
USP10	ubiquitin-specific protease 10
PCa	prostate cancer
WA	Withaferin A
HMGA2	high mobility group A2
FAK	focal adhesion kinase

MMP- 2	matrix metalloproteinase-2
uPA	urokinase-type plasminogen activator
nsP3	non-structural protein 3
HVD	hypervariable domain
MAYV	Mayaro virus
CHIKV	Chikungunya virus
YFV	Yellow fever virus
HCV	hepatitis C virus
L1	LINE-1
L1ORF1p	L1-encoded ORF1 protein
FMDV	foot-and-mouth disease virus
SVV	Seneca Valley virus
EV71	enterovirus 71

Consent for publication

All authors agree to publish this review.

Ethics approval and consent to participate

Not applicable.

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CRediT authorship contribution statement

Jieyu Guo: Writing – original draft, Investigation, Formal analysis. **Rongyi Huang:** Writing – original draft, Formal analysis. **Yan Mei:** Supervision, Investigation, Funding acquisition, Formal analysis. **Siao Lu:** Software, Methodology. **Jun Gong:** Funding acquisition. **Long Wang:** Funding acquisition. **Liqiong Ding:** Funding acquisition. **Hongnian Wu:** Resources, Project administration, Methodology, Investigation, Funding acquisition. **Dan Pan:** Supervision, Resources, Project administration, Investigation, Funding acquisition. **Wu Liu:** Writing – review & editing, Visualization, Supervision, Methodology, Funding acquisition, Formal analysis.

Declaration of competing interest

The authors have declared that no competing interest exists.

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Data availability

No data was used for the research described in the article.

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