Role(s) of G3BPs in human pathogenesis

Chandrani Mukhopadhyay and Pengbo Zhou*

Department of Pathology and Laboratory Medicine, Weill Medical College of Cornell University, New York, NY 10065, USA.

Running Title: Role(s) of G3BPs in human pathogenesis

Corresponding author: Pengbo Zhou, Department of Pathology and Laboratory Medicine, Weill Medical College of Cornell University, New York, NY 10065, USA. e-mail address: pez2001@med.cornell.edu

Number of text pages: 23
Number of tables: 0
Number of figures: 3
Number of references: 163
Number of words in the Abstract: 130
Number of words in the Introduction: 164
Number of words in the Discussion: 6885

Abbreviations

G3BP1 [Ras-GTPase-activating protein (SH3 domain)-binding protein], SPOP (speckle type BTB/POZ protein), SG (Stress Granules)
Abstract

Ras-GTPase-activating protein (SH3 domain)-binding proteins (G3BP) are RNA binding proteins that play a critical role in stress granule (SG) formation. SGs protect critical mRNAs from various environmental stress conditions by regulating mRNA stability and translation to maintain regulated gene expression. Recent evidence suggests that G3BPs can also regulate mRNA expression through interactions with RNA outside of SGs. G3BPs have been associated with a number of disease states, including cancer progression, invasion, metastasis, and viral infections, and may be useful as a cancer therapeutic target. This review summarizes the biology of G3BP including their structure, function, localization, role in cancer progression, virus replication, mRNA stability, and SGs formation. We will also discuss the potential of G3BPs as a therapeutic target.

KEYWORDS

G3BP1, G3BP2, cancer, SPOP, rasputin, stress granule, virus replication

Significance Statement

In this present review, we will discuss the molecular mechanism(s) and functional role(s) of G3BPs in the context of stress granule formation, interaction with viruses, stability of RNA, and tumorigenesis.

1. Introduction

G3BPs [also known as Rasputin (Rin) in Drosophila] are ubiquitously expressed 68 kDa proteins associated with RasGAP’s SH3 domain, an essential Ras signaling component (Parker et al, 1996). Recent studies have raised doubts about the role of G3BP1 as a genuine binding partner of RasGAP (Annibaldi et al, 2011). Additional research is needed to confirm the
interplay between G3BPs and RasGAP. Moreover, G3BPs play a pivotal role in RNA processing, decay, and stress granule (SG) formation, and have been implicated in several disease pathologies such as neurodegenerative disorders, cancer advancement, and viral infections (Alam & Kennedy, 2019). Growing evidence indicates that G3BPs could be promising targets for cancer treatments (Annibaldi et al., 2011; Dou et al., 2016; Wei et al., 2015). In this article, we will discuss the latest developments in the realm of G3BP research, encompassing the functions of G3BPs in cancer advancement, SG formation, RNA stabilization, translational regulation, and viral infections.

2. Structure and function of G3BPs in different cellular processes

In mammals, there are two homologs of G3BP. They are G3BP1 and G3BP2. G3BP2 exhibits two splice variants G3BP2a and G3BP2b. Distinct genes on human chromosomes 5 and 4 encode for G3BP1 and G3BP2, respectively. Structurally, all G3BPs exhibit a similar structure with distinct domains including a nuclear transport factor 2 (NTF2)-like domain at the N-terminus (Suyama et al., 2000), an acidic and proline-rich region (PxxP) (Kang et al., 2021), an RNA recognition motif (RRM) (Nagai et al., 1995) and a C-terminal arginine and glycine rich (RGG) region (Burd & Dreyfuss, 1994) (Figure 1).

2.1 NTF2-like domain (amino acids 1-138): The NTF2-like domain of G3BPs is an important structural and functional element that contributes to the diverse functions of G3BPs including stress response, RNA metabolism, and nucleocytoplasmic transport. This domain exhibits both structural and functional similarity with the small NTF2 protein, which facilitates the transportation of molecules across the nuclear membrane via nuclear pores. (French et al., 2002; Vogensen et al., 2013). Both G3BP1 and G3BP2 are present in the nucleus during serum stimulation, supporting the role of the NTF2-like domain in nuclear transport (Barnes et al., 2002). On the other hand, a separate research, conducted through targeted mutations in G3BP2 revealed that the NTF2-like domain primarily functions in guiding G3BP2 towards the
nuclear envelope rather than impacting its movement within the nucleus. (Prigent et al., 2000). In addition, it has been demonstrated that the NTF2-like domain aids in protein-protein interactions (Kennedy et al., 2001) such as interaction with Caprin1 (Reineke et al., 2015), which can mediate the dimerization of G3BPs (Tourriere et al., 2003), and also the assembly of SG (Yang et al., 2020a). NTF2-like domains also contribute to viral replication by binding to viral motifs and being enlisted by viral replication complexes (Schulte et al., 2016).

2.2 Acidic domain (amino acids 139-220): The acidic domain is a central region of G3BPs that is rich in negatively charged amino acid residues such as aspartic acid and glutamic acid. The domain is a crucial region that plays a key role in mediating protein-protein interactions and regulating various cellular processes, including SG formation. This region can also negatively affect the phase separation of membrane less compartments and regulate biochemical reactions. (Guillen-Boixet et al., 2020).

2.3 PxxP domain (amino acids 221-339): The PxxP domain is a proline-rich region found in many signaling proteins, including G3BPs, and is involved in protein-protein interactions and SG formation. Furthermore, this region is linked to protein interactions and has the ability to target SH3 domains through binding to aromatic amino acids (Booker et al., 1993). G3BP1’s ability to interact with partner proteins is limited due to the existence of three PxxP motifs (Kay et al., 2000), in contrast to G3BP2a and G3BP2b, which possess five and six PxxP motifs respectively (Kennedy et al., 2001). Moreover, according to Reineke and colleagues, the PxxP domain in G3BP is responsible for initiating eukaryotic initiation factor 2a (eIF2a) phosphorylation and SG formation. They also observed that this motif is essential for antiviral activity (Reineke et al., 2015; Reineke & Lloyd, 2015).

2.4 RRM domain (amino acids 340-407): The RRM domain of G3BPs plays a critical role in mediating RNA binding and protein-protein interactions, which are essential for SG formation and other cellular processes involving RNA regulation. The region contains two conserved sequences, RNP1 and RNP2, that engage in interactions with target RNA sequences ranging
from 2-8 nucleotides by utilizing a binding platform formed by beta sheets (Kennedy et al., 2001; Nagai et al., 1995). This RNA recognition and binding domain regulates tumor-related mRNA stability. In addition to interacting with RNA, the RRM can also bind to other proteins (Clery et al., 2008). The variation in RRM between G3BP1 and G3BP2 is the replacement of valines with isoleucines in the RNP-2 region (Kennedy et al., 2001).

2.5 RGG boxes (amino acids 408-465): The RGG domain consists of clusters of arginine-glycine-glycine repeats. This structure enables post-transcriptional modifications and affects the interactions with proteins or RNA. Protein-mRNA interactions may be affected by methylation of arginine residues on RGG box of G3BPs and is important for several cellular process as discussed below. (1) When G3BP1 is methylated at Arg-433, it regulates the mRNA of Ctnnb1 (β-catenin) in a Wnt-dependent manner (Bikkavilli & Malbon, 2011). (2) The methylation of G3BP2 in a Wnt-dependent manner recruits methylated G3BP2 and leads to the formation of supermolecular complexes with disheveled protein 3 (Dvl3-complexes), thereby enabling the phosphorylation of lipoprotein receptor 6 (LRP6) at Ser-149 through GSK3β (Glycogen Synthase Kinase 3 Beta) (Bikkavilli & Malbon, 2011). (3) G3BP2 methylation is also implicated in the regulation of β-catenin mRNA; however, it does not affect the protein (Bikkavilli & Malbon, 2011). (4) The oxidative stress triggered by sodium arsenite prompts the demethylation of G3BP1 at Arg-447, which regulates the assembly of SGs (Tsai et al., 2016). (5) PRMT1 (Protein Arginine Methyltransferase 1) enters SGs and methylates G3BP1 at Arg-477 and stimulates SG disassembly whereas methylation of Arg-435 and Arg-460 by PRMT1 and PRMT5 has no effect during SGs formation (Tsai et al., 2016). (6) During SG formation, Jumonji C domain-containing protein 6 (JMJD6), a constituent of SGs, interacts with G3BP1 and catalyzes its demethylation (Tsai et al., 2016). (7) A recent report suggests that LRP6, a canonical Wnt receptor, suppresses the arginine methylation of several proteins, including G3BP1 (Ramachandran et al., 2018). In addition, the RG-rich domain is also involved in nucleocytoplasmic shuttling (Isabelle et al., 2012) and is essential for virus replication in the host (Gotte et al., 2019).
3. Expression and subcellular localization of G3BPs

Although G3BPs are universally expressed in normal cells, there is some isoform-specific tissue restriction in their expression. For instance, G3BP1 is primarily expressed in the lung and kidney, G3BP2a in the brain, and G3BP2b in the small intestine (Kennedy et al., 2001). Although G3BPs are mainly cytoplasmic proteins, they can translocate to the nucleus by virtue of the NTF2-like domain, which is responsible for their nuclear localization (Smith et al., 1998). Costa and colleagues isolated G3BP1 from nuclear extract of HeLa cell as a functional DNA and RNA helicase indicating the nuclear localization of G3BP1 (Costa et al., 1999). We have also observed, in multiple experiments and models, that G3BP1 is present in both the cytosol and nucleus, suggesting shuttling between these compartments (Mukhopadhyay et al., 2021). As a result of its phosphorylation at Ser-149, G3BP1 can move to nuclei in quiescent cells (Gallouzi et al., 1998; Tourriere et al., 2001) whereas G3BP2 can move to nuclei in response to serum stimulation (French et al., 2002).

4. Regulation of G3BPs at transcriptional, translational and post-translational levels

It is known that G3BP1 is subject to transcriptional, translational, and post-translational regulation. The regulation of G3BP1 has a wide range of downstream effects, including the assembly of SGs (Zhang et al., 2019a) and the promotion of tumors (Alam & Kennedy, 2019). Studies investigating the transcriptional regulation of G3BP1 are limited. Using gene set enrichment analyses (GSEA), Ali and colleagues identified YY1 (Yin Yang 1 transcription factor), SYK (Spleen Associated Tyrosine Kinase), E2F-1 (E2F transcription factor 1), FOXA1 (Forkhead Box A1) and TGFBR2 (Transforming Growth Factor Beta Receptor 2) as activators of G3BP1 gene transcription, while SRF (Serum Response Factor), SIN3A (SIN3 Transcription
Regulator Family Member A), and AKT-1 (AKT Serine/Threonine Kinase 1) as suppressors (Ali et al, 2021).

Several proteins and miRs regulate G3BP1 at the post-transcriptional level. Many of these proteins interact with 5'-untranslated region (5'-UTR) (Hoftman et al, 2008; Lee et al, 2020; Somasekharan et al, 2015) of G3BP1, than with 3'-untranslated region (3'-UTR) (Deng et al, 2015; Liu et al, 2021; Lv et al, 2017). In contrast, many miRs have been identified to bind the 3'-UTR of G3BP1 and subsequently downregulate its expression. Y-box binding protein 1 (YB-1) is a DNA/RNA binding protein that binds to the 5'-UTR of G3BP1 transcripts and regulates translation (Somasekharan et al., 2015). Thus, YB-1 regulates G3BP1 availability for SG assembly (Zhang et al., 2019a) and there is a strong association between YB-1 and G3BP1 expression in human sarcomas (Somasekharan et al., 2015). Lee and colleagues showed that Melanoma-associated antigen gene B2 (MAGE-B2), which is normally found in testicular tissue but is abnormally expressed in tumors (Hoftman et al., 2008), can interact with the 5'-UTR of G3BP1. This interaction results in increased translation of G3BP1 (Lee et al., 2020). The TAR DNA-binding protein 43 (TDP-43), which binds directly to highly conserved cis-regulatory elements found in the 3'-UTR of G3BP1, stabilizes the mRNA (Sidibe et al, 2021). Recent studies have identified G3BP1 interacting miRs, such as miR-193a-3p, miR-129-5p, miR-622, miR-132, and miR-362-3p (Deng et al., 2015; Liu et al., 2021; Lv et al., 2017).

G3BP1 undergoes various post-translational modifications, including but not limited to methylation (Tsai et al, 2017), phosphorylation (Reineke et al, 2017), acetylation (Gal et al, 2019), polyADP-ribosylation (pADPr) (Leung et al, 2011), and ubiquitination (Gwon et al, 2021). These post-translational modifications of G3BP1 are often necessary for the disassembly of SGs rather than their assembly (Gwon et al., 2021). One example is the modification of G3BP1 by the PRMT, arginine methyltransferase, which can methylate residues Arg-435, Arg-447, and Arg-460. (Tsai et al., 2017). In the same vein, the acetylation of lysine 376 of G3BP1 by CBP/P300, which is a transcription co-factor for various nuclear proteins, results in the
disruption of RNA binding by G3BP1. This disruption leads to the disassembly of SGs (Gal et al., 2019). Similarly, G3BP1 Ser-149 is phosphorylated by casein kinase 2 (CK2) both in vivo and in vitro, which inhibits SG assembly (Reineke et al., 2017). As per Tsai et al.’s findings, JMJD6 augments the formation of SGs by reducing the monomethylation of G3BP1 and the asymmetric dimethylation of its three arginine residues (Tsai et al., 2017). Moreover, Gal and colleagues confirmed that the same residue of G3BP1 is targeted for deacetylation by HDAC6 (histone deacetylase 6) as is targeted for acetylation by CBP/P300. G3BP1 is excessively acetylated when HDAC6 is lost or inhibited, resulting in impaired SG induction (Gal et al., 2019). Additionally, poly-ubiquitinated G3BP1 at Lys-63 regulates the disassembly of SGs (Gwon et al., 2021). Conversely, specific post-translational modifications of G3BP1 aid in the formation of SGs. One example of a post-translational modification that promotes the assembly of SGs is the methylation of G3BP1 by PRMT5, which preferentially targets Arg-460 to enhance G3BP1 signaling and SG formation (Tsai et al., 2016). Just like the previous instances, the modification of G3BP1 by pADPr polymerase (PARP) can trigger the assembly of SGs (Leung et al., 2011).

In addition to its role in regulating SG assembly, post-translational modification of G3BP1 is also involved in a variety of other physiological functions. The PRMT1 mediates methylation of G3BP1 Arg-435, releases β-catenin mRNA and activates Wnt signaling (Bikkavilli & Malbon, 2011). Additionally, dexamethasone or ginsenoside-Rg1 activates the glucocorticoid receptor (GR), resulting in the rapid phosphorylation of G3BP1, facilitating its transfer from the cytoplasm into the nucleus (Kwok et al., 2017).

Regulation of G3BP2 also occurs at the transcriptional, translational, and posttranslational modification levels. At transcriptional level, AR (androgen receptor) and FOXD1 (Human Forkhead-box D1) can bind to the G3BP2 promoter and modulate its transcription (Ashikari et al, 2017; Hannenhalli & Kaestner, 2009; Heinlein & Chang, 2004; Kanda et al, 2014; Lin et al, 2020). At translational level, miRNAs targeting the 3'UTR of G3BP2 generally decrease its translation (Carney, 2016; Guo et al, 2021; Zhao et al, 2016; Zhao & He, 2021) while binding to
the 5'UTR of G3BP2 enhances its expression (Bezzi et al., 2017; Liu et al., 2018, 2020). There are various post-translational modifications of G3BP2. PRMTs target the RGG domain of G3BP2 in response to Wnt3a, leading to its methylation. The methylated form of G3BP2 serves as a positive regulator of Wnt signaling (Bikkavilli & Malbon, 2011; Jamieson et al., 2014; Katoh & Katoh, 2009; Li et al., 2012). The stability of G3BP2 protein is preserved through de-ubiquitination by the USP10 (Matsuki et al., 2013; Soncini et al., 2001; Takayama et al., 2018).

5. Roles of G3BPs in stress granule formation

When cells are exposed to cellular stresses such as oxidative stress, hypoxia, or viral infections, SG are formed in the cytoplasm. These SGs are primarily composed of complexes of mRNA and proteins that have been halted in their translation (Anderson et al., 2015; Buchan & Parker, 2009; White & Lloyd, 2012). Under stress conditions, SGs protect mRNA (Kedersha & Anderson, 2002) although their precise role in protein retrieval is not fully understood, studies have indicated that SGs also recruit proteins associated with diverse signaling pathways that can influence cellular metabolism and survival. Thus, SGs likely have additional functions beyond their role in mRNA storage and translational control. (Kim et al., 2005; Li et al., 2004). Under conditions of stress-induced eIF2a activation, both G3BP1 and G3BP2 localize within SGs (Tourriere et al., 2003), but they are also capable of forming SGs independently (Matsuki et al., 2013). G3BPs are phosphorylated under normal conditions and promote mRNA degradation. When cellular stress occurs, such as treatment with arsenite, unphosphorylated G3BPs oligomerize and deliver mRNA to SGs. When mammalian cells are treated with arsenite, G3BPs are found to be unphosphorylated at Ser-149, which results in the formation of SGs (Tourriere et al., 2003) (Figure 2). The findings of these studies imply that the formation of SGs is a finely controlled process that is regulated in response to cellular stress. Besides stress-inducing agents, overexpression of several RNA-binding proteins such as TIA-1 (TIA1 Cytotoxic Granule Associated RNA Binding Protein), CPEB1 (Cytoplasmic Polyadenylation Element
Binding Protein 1) and G3BPs in combination with inhibition of translational initiation complex components (Dang et al, 2006; Mazroui et al, 2006) can induce the assembly of SGs (Gilks et al, 2004; Tourriere et al., 2001; Wilczynska et al, 2005). Unlike other stress-inducing agents, the induction of SGs by G3BPs was found to be independent of eIF2α phosphorylation but dependent on PKR-mediated phosphorylation of eIF2a (Reineke et al, 2012). However, Taniuchi and colleagues demonstrated that the C-terminal region of G3BPs can induce phosphorylation of eIF2a (Taniuchi et al, 2011a). Therefore, it remains to be elucidated if specific cellular contexts determine the dependence of eIF2a phosphorylation by G3BPs. The formation of SGs in response to different stress stimuli is influenced by the interplay between G3BP's own transcript and/or protein and other proteins. McDonald and colleagues demonstrated that TDP-43 regulates SG by controlling the aggregation of TIA-1 and the mRNA levels of G3BP1. Specifically, when TDP-43 was silenced, it prevented the aggregation of TIA-1 and reduced the mRNA levels of G3BP1 (McDonald et al, 2011). Furthermore, YB-1 regulated the expression levels of G3BP1 through its interaction with the 5'-UTR of G3BP1, resulting in the formation of SGs during stress (Somasekharan et al., 2015) (Figure 2a). Caprin1 can form a complex with G3BP1, and this complex is found in SGs (Figure 2a). However, it is not essential for the sequestration or formation of Caprin1 and G3BP1 into SGs, as they can still accumulate in SGs even in the absence of their association. (Solomon et al, 2007). However, Kedersha and colleagues reported that the interaction of G3BP1 with Caprin1 or USP10 (Ubiquitin Specific Peptidase 10) determined the fate of SGs as the former induced SGs formation while the later induced SGs inhibition (Kedersha et al, 2016). So far, based on published literature, it is considered that G3BPs are the basic components of SGs necessary for SG formation. Under stress conditions, G3BP2 may undergo dephosphorylation at Ser-149, leading to enhanced homo- and hetero-multimerization with G3BP1 and initiation of SG formation. The acidic region of both G3BP1 and G3BP2 has been shown to inhibit SG formation (Matsuki et al., 2013;
Tourriere et al., 2003). While G3BP2 can induce SG formation even in the absence of stress, its activity is lower compared to that of G3BP1 (Matsuki et al., 2013).

It has recently become clearer how G3BPs contribute to the formation of SGs. It has been reported that SGs form in response to stress through liquid-liquid phase separation (LLPS), creating dynamic and membrane-less condensates (Maruri-Lopez et al., 2021). Recently, Taylor and colleagues reported that NTF2 domain of G3BP1 dimerizes under normal conditions and generates a "locked conformation". However, under stressed conditions unfolded RNA interacts with the acidic and PxxP domains of G3BPs and generates an "open conformation" that allows interaction with other RNAs. This allows the G3BPs-RNA complex, which then recruits other stress proteins and forms a multimeric complex "SG" (Guillen-Boixet et al., 2020; Sanders et al., 2020; Yang et al., 2020a) (Figure 2a). In line with this, according to Taylor and colleagues, the main structural difference between G3BP1 and G3BP2 is in their internal regions, which are not essential for SG formation (Yang et al., 2020a). G3BP2 has predicted phosphorylation sites at Ser-149 and Ser-232, suggesting that it can also shift between open and closed conformational states like G3BP1. However, Franzmann and colleagues found that the phase separation properties of G3BP2 are slightly different from those of G3BP1. This group showed that G3BP2 has a higher tendency to phase separate with proteins and RNA compared to G3BP1 (Guillen-Boixet et al., 2020). This may be due to G3BP2's longer intrinsically disordered regions and RNA-binding domain compared to G3BP1. Overall, it is not clear yet how these SGs contribute to disease progression, such as oncogenesis or drug resistance. Even though few articles mentioned SGs are involved in potential drug resistance mechanism (Gong et al., 2013; Sabile et al., 2013; Shi et al., 2019; Somasekharan et al., 2022), but future studies may explore detail mechanism within this perspective.

6. Contribution of G3BPs in cancer
G3BPs promotes tumor cell proliferation by attenuating the function of tumor suppressor genes. A number of human cancers overexpress G3BP1 and/or G3BP2, including breast cancer (Barnes et al., 2002; Guitard et al., 2001; Marx, 1989), pancreatic cancer (Taniuchi et al., 2011b), colon, head and neck, lung (French et al., 2002; Guitard et al., 2001), and prostate cancer (Ashikari et al., 2017; Mukhopadhyay et al., 2021; Mukhopadhyay C, 2019; Takayama et al., 2018).

6.1 G3BP1 driven molecular mechanism of cancer progression

Parker and colleagues reported that G3BP1 promotes tumor cell proliferation by activating the Ras signaling pathway (Parker et al., 1996). However, a recent study found no direct interaction between G3BP1 and Ras-GAP, which suggests that G3BP1 may not dysregulate RAS signaling by directly targeting Ras-GAP (Annibaldi et al., 2011). Numerous studies have indicated that G3BPs play a role in regulating cancer cells and act as accessory genes that support the survival of cancer cells Figure 2. Huang and colleagues observed that PTEN has the ability to downregulate the expression of G3BP1 protein via the PI3K pathway by virtue of its phosphatase activity (Huang et al., 2005). Therefore, it is conceivable that loss of PTEN function resulting in the overexpression of G3BP1 leads to induce cellular proliferation and dysregulated promotion of the cell cycle (Figure 2a). Binding of G3BPs to the tumor suppressor p53 leads to its translocation from the nucleus to the cytoplasm, resulting in the inactivation of p53 (Figure 2a). This step is considered crucial in human tumorigenesis (Kim et al., 2007). G3BP2 interacts with its negative regulator MDM2 (murine double minute 2), and exports p53 from the nucleus to the cytoplasm (Kim et al., 2007). In a separate study, Mao and colleagues observed that a cytosolic long intervening/intergenic noncoding RNAs, P53RRA, functions as a tumor suppressor by activating the p53 pathway. Their findings showed that P53RRA interacts with the RRM domain of G3BP1 in the cytoplasm through nucleotides 1 and 871. This interaction displaced p53 from the G3BP1 complex, thereby keeping p53 in the nucleus, which led to cell cycle arrest and cell death (Mao et al., 2018). Additionally, G3BP2 is involved in regulating the
translocation of p53 from the nucleus to the cytoplasm by interacting with the SUMO-E3 ligase RanBP2 when androgen is induced resulting in tumor formation (Ashikari et al., 2017).

G3BP1 has been found to play a role in the progression of breast cancer and esophageal cancer by inhibiting the degradation of beta-catenin and enhancing its stability, thereby promoting cell proliferation (Zhang et al., 2021a; Zhang et al., 2019b). However, some studies suggest that G3BP1 actually has a negative regulatory effect on the Wnt/β-catenin signaling pathway, which leads to a decrease in β-catenin levels and an increase in G3BP1 expression (Bikkavilli & Malbon, 2011). In addition, G3BP1 has been shown to bind to the tuberous sclerosis complex (TSC) and inhibit mTORC1 signaling, which can otherwise drive the growth and migration of breast cancer cells (Prentzell et al., 2021).

G3BP1 has been shown to contribute to the proliferation, migration, and invasion of renal cell carcinoma (RCC), and knockdown of G3BP1 has been found to block the IL-6/STAT3 signaling pathway and reduce the metastatic ability of RCC (Wang et al., 2018). In addition, G3BP1 has been found to interact with Y-box binding protein 1 (YBX1) to upregulate the expression of secreted phosphoprotein 1 (SPP1) and activate nuclear factor-κB (NF-κB), ultimately promoting RCC metastasis (Wang et al., 2018). Moreover, G3BP1 has been implicated in promoting resistance to sunitinib in RCC (Sonnhof et al., 1975). These findings suggest that targeting G3BP1 may be a promising therapeutic strategy for the treatment of RCC (Cho et al., 2019).

In human lung cancer (H1299) cells, knockdown of G3BP has been found to inhibit the activation of Src, focal adhesion kinase (FAK), and ERK1/2, while also reducing the expression of NF-κB. This leads to a decrease in the expression levels of matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), and urokinase-type plasminogen activator (uPA), ultimately inhibiting the proliferation, invasion, and migration of lung cancer cells (Zhang et al., 2013). Additionally, G3BP1 has been shown to be necessary for the activation of the senescence-associated secretory phenotype (SASP) (Omer et al., 2020). The impact of SASP
on the proliferation and migration of cancer cells is complex and not well understood (Rao & Jackson, 2016).

According to reports, the strong cytoplasmic localization of p53 is associated with an increase in G3BP2 expression in prostate cancer (Ashikari et al., 2017). This correlation predicts a poor prognosis and a higher likelihood of progression to hormone-refractory disease. These findings suggest that G3BP2 plays a role in the progression of prostate cancer (Ashikari et al., 2017). A recent study showed that TRIM25 functions through interaction with G3BP2 to downregulate p53 activity resulting in prostate cancer cell proliferation (Takayama et al., 2018). Moreover, Takayama and colleagues observed that the deubiquitinase USP10 regulates androgen-mediated signaling. It has been observed that the interaction between USP10 and G3BP2 leads to the suppression of p53 signaling, correlating to a poor prostate cancer prognosis. These findings emphasize the oncogenic function of USP10 in prostate cancer through its interaction with G3BP2 (Takayama et al., 2018).

Recently, we observed that G3BP1 as an interactor and upstream regulator of CUL3SPOP, functioning as an inhibitor of CUL3SPOP ubiquitin ligase. This reveals a distinct function of G3BP1 that abrogates CUL3SPOP tumor suppressive role of CUL3SPOP and promotes prostate tumorigenesis (Mukhopadhyay et al., 2021) (Figure 2a). Mechanistically, G3BP1 competitively inhibits substrate binding to SPOP and accelerates prostate epithelial cell proliferation, migration and invasion. As such, silencing of G3BP1 by CRISPER-Cas9 significantly reduced organoid formation of mPECs (murine prostate epithelial cells) and tumorigenicity in a prostate cell line-derived xenograft tumor model. Moreover, we showed that G3BP1 is a bona fide target of an AR that upregulates G3BP1 transcription and sets up a feed-forward loop of AR-mediated adverse signaling that further exacerbates PCA progression (Mukhopadhyay et al., 2021; Mukhopadhyay C, 2019). This study shed light on new mode of SPOP inactivation other than SPOP mutation.
6.2 Role of G3BPs in cancer metastasis, invasion and Epithelial to mesenchymal transition (EMT) phenotype

The degradation of Binder of Arl Two (BART) transcripts is facilitated by G3BP1, while CD24 interacts with G3BP1 to inhibit its endoribonuclease activity on BART within SGs (Figure 2a). This mechanism prevents the metastasis and invasion of pancreatic cancer cells (Taniuchi et al., 2011a). The dominant-negative overexpression of the N-terminal domain of G3BP1 suppresses the binding of G3BP1 and BART, thereby influencing the posttranscriptional control of cell invasiveness and metastasis in pancreatic cancer cells (Taniuchi et al., 2011b). In addition, silencing of G3BP1 by RNAi led to a decrease in the spread and infiltration of lung cancer cells in humans. This was achieved by reducing the levels of Src, FAK, ERK, and NF-κB through the MEK/ERK pathway, which in turn led to a decrease in the activation of matrix metalloprotease (MMP) 2 and 9, as well as plasminogen activator (uPA) (Zhang et al., 2013) (Figure 2a). Therefore, silencing of G3BPs may attenuate the signaling cascades responsible for invasion and metastasis. In esophageal squamous cell carcinoma, Wang and colleagues observed that G3BP1 may have a crucial function in promoting lymph node metastasis and invasiveness. This is thought to occur through the activation of both the PI3K/AKT/mTOR and Wnt signaling pathways (Zhang et al., 2019b). G3BP1 was found to inhibit lung metastasis by inhibiting SG formation in a lung cancer mouse model (Somasekharan et al., 2015).

Epithelial to mesenchymal transition (EMT) is one of the hallmarks of cancer (Hanahan & Weinberg, 2011). The SMAD signaling pathway appears to be involved in the promotion of EMT in breast cancer cells as a result of G3BP1 overexpression (Zhang et al., 2015). Knockdown of SMADs by siRNA completely inhibited G3BP1-induced EMT, indicating that the SMAD signaling pathway participates in this process (Figure 2a). Studies have indicated that reducing G3BP1 expression can prevent MDA-MB-231 cells from displaying mesenchymal characteristics in vitro, as well as impede tumor growth and metastasis in 4T1 cells in vivo. These findings suggest that targeting G3BP1 could be a promising therapeutic strategy for treating metastatic
breast cancer. G3BP1 activates EMT factors through phosphorylation of SMAD (Zhang et al., 2015). In both in vitro and in vivo settings, researchers have demonstrated that the reduction of G3BP1 leads to decreased cell migration and metastasis in hepatocellular carcinomas (HCCs) (Gupta et al., 2017). Research has indicated that G3BP2 plays a role in the initiation of breast cancer by stabilizing mRNA transcripts of the squamous cell carcinoma antigen recognized by T cells 3 (SART3). The SART3 gene increases the expression of the pluripotent transcription factors octamer binding protein 4 (Oct-4) and Nanog Homeobox (Nanog) (Gupta et al., 2017) (Figure 2b). An anticancer compound, C108, interacts with G3BP2 via its RRM domain and inhibits tumor growth by degrading SART3 mRNA (Gupta et al., 2017). According to a recent study, G3BP2 acts as both a positive regulator in the initiation of breast cancer and a negative regulator in its metastasis (Gupta et al., 2017). One possible explanation for the opposing roles of G3BP2 is that cancer cells need to shed their EMT-phenotype to acquire cancer-initiating properties necessary for metastatic colonization (Ocana et al., 2012). Recently, Shuang and colleagues observed that G3BP2 is significantly overexpressed in osteosarcoma cells and that FGA5-AS1 plays a role in promoting osteosarcoma cell proliferation and invasion by acting as a competing endogenous RNA (ceRNA) to sequester miR-124-3p and upregulate the expression of G3BP2 (Shuang et al., 2022).

6.3 G3BP1 affects tumor growth by regulating mRNA stability

Controlling mRNA stability is crucial in regulating gene expression during cell proliferation, differentiation, and development. G3BP1 interacts with RNA and determine its stability. It has been reported that G3BP1 interacts with c-Myc mRNA and, through its endoribonuclease activity, it cleaves the 3′-UTR of the c-Myc mRNA in a phosphorylation-dependent manner in vitro. However, this finding was not supported by other studies (Gallouzi et al., 1998; Tourriere et al., 2001; Zekri et al., 2005) where they used MEF cells isolated from G3BP1 knock out mice. There is a possibility that G3BP2 is still present in these cells, and it is uncertain whether there are functional redundancies between these proteins in regulating c-Myc mRNA. Additionally, it is
possible that under these conditions, the endoribonuclease activity of G3BP1 is incapable of degrading short-lived mRNAs like the c-Myc transcript. Altogether, stability of c-Myc mRNA by G3BP1 is still ambiguous and requires further investigation. However, the endoribonuclease activity of G3BP1 is further supported by the stability of other transcripts such as BART (Taniuchi et al., 2011a), CTNNB1 (Bikkavilli & Malbon, 2011), PMP22 (Winslow et al., 2013), IGF-II and GAS5 (Zekri et al., 2005) TAU (Atlas et al., 2004) and CDK7 (Lypowy et al., 2005) (Figure 2a). Ortega and colleagues reported that G3BP1 interacts with beta-F1 mRNA, mitochondrial H(+) -ATP synthase subunit and inhibits its translation, which may be involved in cancer progression (Ortega et al., 2010). In a recent study by Fisher and colleagues, it was discovered that the RNA decay machinery proteins Up-frameshift 1 (UPF1) and G3BP1 play essential roles in the degradation of highly structured mRNAs with long 3'UTRs. (Fischer et al., 2020). The regulation of mRNA transcription by G3BP1 is intricately controlled and relies on post-transcriptional modifications as well as its interaction with other proteins. For example, G3BP1 interacts with CDK7 and CDK9 mRNA transcripts in the presence of filamin for their stabilization (Lypowy et al., 2005). G3BP1 exhibits its endoribonuclease activity in a phosphorylation-dependent manner (Irvine et al., 2004). So far, there is only one report suggesting a role for G3BP2 in stabilizing mRNA. Gupta and colleagues observed that SART3 mRNA was stabilized by G3BP2 resulting in increased expression of the pluripotent transcription factors Oct-4 and Nanog which are involved in tumor initiation in breast cancer cells (Gupta et al., 2017) (Figure 2b).

7. Contributions of G3BPs in other diseases

G3BP1’s most acknowledged function is its contribution to the initiation of SGs. Additionally, it has been associated with neurodegenerative disease through various proposed mechanisms (Li et al, 2013). Firstly, the failure of SGs to assemble correctly may lead to neurodegeneration
(Wolozin & Ivanov, 2019). Secondly, the persistence of SGs can lead to the development of cytoplasmic aggregates, a common feature observed in neurodegenerative disorders (Baron et al., 2013). Finally, the inability to disassemble SGs may sequester vital translation factors, transport proteins, or other critical cellular chaperones (Wolozin & Ivanov, 2019). Newly published articles have highlighted the significant role of G3BP1 in the regulation of cardiac hypertrophy, atrial fibrillation, and coronary heart disease (Dong et al., 2019; He et al., 2015; Xia et al., 2020). It has been reported that G3BP1/RIG-I/MAVS relay pathway is a component of the Wnt signaling pathway and targeting Wnt signaling may help reduce atherosclerosis, a disease of the arteries due to the deposition of fatty material on the inner walls (Ramachandran et al., 2018).

8. Roles of G3BPs in viral infection

The specific function of G3BPs in the context of viral infection has yet to be fully understood. Some studies have demonstrated that viruses exploit G3BPs to aid in their replication or transcription. On the other hand, other research has shown that G3BPs activate the innate immune system in response to viral infection to safeguard host cells against virus replication. In the following sections, each of these processes will be discussed (Figure 2a).

8.1 G3BPs promote virus replication

Vaccinia virus (VV), a DNA virus, utilizes G3BP1 to promote its replication in host cells (Katsafanas & Moss, 2004). During the initial stages of infection, the virus becomes enveloped by the rough endoplasmic reticulum, which attracts essential translation-initiating factors (including G3BP1 and Caprin-1). This enhances the activity of viral RNA polymerase and transcription factors, ultimately promoting viral replication (Katsafanas & Moss, 2004). G3BP1 also promotes the replication of different RNA viruses. Negative strand synthesis of the +SSRNA chikungunya viral genome is regulated by G3BP1 and/or G3BP2 (Scholte et al., 2015).
The study reveals that the interaction between G3BPs and nsP2 can facilitate CHIKV RNA replication and recover the infectivity of viruses that do not contain G3BP-binding motifs in the HVD of nsP3 (Wang & Merits, 2022). To promote the efficient translation of Sindbis virus (SINV) mRNA, G3BP1 interacts with both the nsP3 (non-structural protein 3) and the 40S ribosomal subunit (Gotte et al., 2019). The RNA-binding protein farnesoid X receptor (FXR) from Eastern equine encephalitis virus (EEEV) and Venezuelan equine encephalitis virus (VEEV) interacts with G3BP1 and/or G3BP2 and nsP3 proteins to construct the viral replication complex (vRC) (Frolov et al., 2017; Kim et al., 2016). The binding sites of the G3BP and FXR protein families in the nsP3 HVD (hypervariable Domain) of EEEV are deleted, the virus becomes unable to cause disease in mice (Meshram et al., 2020). Hepatitis C virus (HCV), dengue virus (DENV), rubella virus (RUBV), and Newcastle disease virus (NDV) interact with G3BP1 and/or G3BP2 to facilitate either their replication or their transcription (Bidet et al., 2017; Matthews & Frey, 2012; Sun et al., 2017; Xia et al., 2015; Yi et al., 2006). The bursal disease virus (IBDV) exploits G3BPs to trigger the development of multiple SGs, facilitating the virus's replication within the host cell (Zhao et al., 2020). Based on published reports, roles of SGs differs in virus-infected cells. As an illustration, the formation of SG enhances viral replication in the case of respiratory syncytial virus (RSV) infection (Lindquist et al., 2010). However, the assembly of SGs inhibits Zika virus (ZIKV) infection (Hou et al., 2017), while the creation of SGs has no impact on viral replication during rubella virus (RUBV) infection (Matthews & Frey, 2012). Recently, it has been reported that G3BP1 and G3BP2 promote the viral growth of Mayaro virus (MAYV), which is belong to the group of Old World alphaviruses (Neyret et al., 2022).

The current pandemic of COVID-19 (Coronavirus Disease-2019), a respiratory disease, has led to over millions of deaths in over 188 countries. COVID-19 is caused by a novel virus strain, SARS-CoV-2, an enveloped, positive-sense, single-stranded RNA beta-coronavirus of the family Coronaviridae (Wang et al., 2020; Zhu et al., 2020). In 2020, the interactome study by Gordon et. al., identified SARS-CoV-2 nucleocapsid (N) protein, which is critically involved in
viral RNA replication, binds to G3BP1, which is later supported by many other groups (Biswaletal, 2022; Gordonetal, 2020; Liu et al., 2022). Recently, it has been reported that SG assembly, which is a defense mechanism and protects cells in any stress condition (Dolliver et al., 2022; Liu et al., 2022), was significantly reduced upon SARS-CoV-2 infection (Liu et al., 2022). They also observed that N protein of SARS-CoV-2 inhibit G3BP1-RIG-I-mediated interferon (IFN) production to facilitate viral replication (Liu et al., 2022). According to these studies, G3BP1 can turn as a "promiscuous" regulator of SARS-CoV-2 infection and thus targeting G3BP1 may be used as a new therapeutic strategy for SARS-CoV-2 virus infection.

8.2 G3BPs inhibit virus replication

Both DNA and RNA virus replications are inhibited by G3BPs. Liu and colleagues reported that G3BP1 facilitated the binding between cGAS (Cyclic GMP-AMP Synthase) and DNA to form a large cGAS complex that induced cGAS-dependent IFN production. Therefore, G3BP1 plays a critical role in combating DNA virus infections by engaging in the cGAS-mediated antiviral response (Liu et al., 2019). G3BPs also antagonize RNA virus growth. For instance, G3BP interacts with various viral proteins of porcine epidemic diarrhea virus (PEDV), foot-and-mouth disease virus (FMDV), mammalian reovirus (MRV), and porcine reproductive and respiratory syndrome virus (PRRSV), thus inhibiting their propagation in the host cell (Catanzaro & Meng, 2019; Choudhury et al., 2017; Galan et al., 2017; Pandey et al., 2019). It has also been reported that FMDV suppresses the host's stress and antiviral responses, and highlights the significance of G3BP1 dephosphorylation and its breakdown by viral protease in hindering the host's ability to defend against FMDV infection (Ye et al., 2018). G3BP1 is an antiviral protein (Reineke & Lloyd, 2015), as such, viral proteins cleave G3BP to initiate antiviral responses. For an example, 3Cpro of coxsackie virus type B3 (CVB3) (Fung et al., 2013), human enterovirus D68 (EV-D68) (Cheng et al., 2020) and poliovirus (PV) can cleave G3BP1 at Gln-325, resulting in the disassembly of SGs, which aids in viral translation. G3BP1 promotes the expression of RIG-I and positively regulates type-1 interferon (IFN1) response to generate antiviral responses (Yang et al., 2022).
et al, 2020b). Furthermore, G3BP1 facilitates the generation of cytokines through activation of the NF-κB and c-Jun N terminal kinase (JNK) signaling pathways (Reineke & Lloyd, 2015), to generate an antiviral response (Wen et al, 2020; Zhou et al, 2021). G3BP inhibits the replication of retroviruses. As an illustration, G3BP1 seizes HIV-1 RNA transcripts, which restricts viral protein production, mRNA translation, and virus particle formation (Cobos Jimenez et al, 2015). Nevertheless, the capsid domain of HIV-1 Gag protein can also interact with G3BP1, leading to the disassembly of preformed SGs by replacing eEF2. This response may facilitate virus replication (Valiente-Echeverria et al, 2014).

9. G3BPs as potential therapeutic targets

There is increasing evidence that G3BPs plays a role in oncogenesis, autoimmune diseases, and viral infection. In the following sections, we summarize the latest articles describing G3BPs as a potential therapeutic targets.

9.1 Cancer-related therapeutic treatments

Currently a combination of resveratrol, epigallocatechin gallate (EGCG) and GAP161 has been shown to target G3BP1 and inhibit its carcinogenic effects (Oi et al, 2015; Shim et al, 2010; Zhang et al., 2013). By interacting with USP10, a deubiquitinating enzyme of p53, G3BP1 negatively regulates the expression of p53, thus controlling melanoma cell proliferation and colon cancer cell proliferation (Oi et al., 2015). Resveratrol directly binds to G3BP1, which leads to the disruption of G3BP1/USP10 interaction. As a result, USP10 is released, allowing for the deubiquitination of p53 and triggering of apoptosis in tumor cells (Oi et al., 2015). Therefore, resveratrol, which is found in natural products, is considered a promising anticancer agent that specifically targets G3BP1.

EGCG, a polyphenol compounds present in green tea, was found to interact with G3BP1 with high binding affinity and thus inhibiting MAPK-mediated signaling to suppress growth of H1299
and CL13 lung cancer cells, where G3BP1 expression is high (Shim et al., 2010). Cho and colleagues reported that lung cancer cell lines become more susceptible to radiation therapy when G3BP1 is depleted. This impact is associated with the production of reactive oxygen species (ROS) (Cho et al., 2019). In colon cancer cells, a novel peptide, GAP161, inhibited MAPK signaling by interfering with the G3BP1 and RasGAP interaction to suppress Ras signaling pathways (Zhang et al., 2012). Furthermore, reducing the levels of G3BP enhances the effectiveness of cisplatin-induced apoptosis and growth inhibition in HCT116 cells (Zhang et al., 2012), indicating that GAP161 could be a promising therapeutic agent for colon cancer.

G3BP1’s ability to regulate the assembly of SGs in cancer cells can affect the efficacy of commonly used clinical drugs like Bortezomib. Bortezomib-induced SG assembly can lead to resistance to Bortezomib-mediated apoptosis, highlighting the importance of G3BP1 in cancer progression (Fournier et al., 2010). Bittencourt and colleagues found that G3BP1 knockdown in U87 glioblastoma cells diminished SG formation and stimulated Bortezomib-induced apoptosis in vitro, in addition to inhibiting glioblastoma-induced angiogenesis in vivo (Bittencourt et al., 2019).

There are few reports on the therapeutic treatment of G3BP2 alone. As G3BP1 and G3BP2 share common domains and most of the drugs target the NTF2 domain of G3BPs, which is similar in both G3BP1 and G3BP2. As such, compounds/drugs used to treat G3BP1 can also be used to treat G3BP2. In the following section we discuss the therapeutic treatment options for G3BP2. There are two peptides (P109 and P110) that can inhibit the interaction between NTF2 domain of G3BPs and Ras-GAP and biologically involve in cisplatin-induced cellular death (Cui et al., 2010). Additionally, it has been reported that compound C108 inhibits G3BP2, delays stress response, suppresses cancer cell metastasis, and promotes the proliferation and infiltration of CD8 T-cells (Gupta et al., 2017; Zhang et al., 2021b; Zheng et al., 2022).

9.2 Therapeutic treatments for other diseases
G3BP1’s participation in signaling pathways associated with innate immunity indicates its potential involvement in autoimmune diseases. G3BP1 is recognized for its involvement in the identification of foreign DNA by cGAS. However, when G3BP1 is excessively activated, it can trigger the overproduction of IFN via cGAS, which can result in autoimmune diseases (Liu et al., 2019). Efficient activation of cGAS, a key component of DNA sensing, relies on the critical involvement of G3BP1. G3BP1 assists in the formation of significantly large cGAS complexes, which amplifies cGAS’ capability to bind to DNA. Conversely, deficiency in G3BP1 leads to inefficient DNA binding by cGAS, resulting in reduced cGAS-dependent IFN production. In this regard, EGCG has been discovered to interrupt the G3BP1-cGAS complex, thereby obstructing DNA-triggered activation of cGAS. This leads to the inhibition of IFN production both in vivo and in vitro (Liu et al., 2019). Resveratrol inhibits the production of IFN triggered by intracellular DNA and RNA by targeting G3BP1 (Cai et al, 2021). Given their ability to disrupt the G3BP1-cGAS complex and inhibit IFN production, both EGCG and resveratrol hold promise as potential treatments for autoimmune diseases related to cGAS or caused by abnormal nucleic acid sensing.

10. Concluding Remarks and Further Perspectives

G3BPs have emerged as important molecules in various pathological conditions like oncogenesis and viral infection. Current evidence suggest that G3BPs are highly expressed in cancer, and thus, could be extremely useful in either detection or prognosis of cancer patients. Furthermore, G3BPs, particularly G3BP1, have emerged as promising targets for drug development and cancer therapy. G3BPs engage in numerous interactions with various proteins to regulate a wide range of biological processes. Targeting these protein interactions may present a promising opportunity for developing novel therapeutic strategies in various disease states. While the crystal structure of G3BP1’s NTF2 domain has been determined, the complete molecular architecture of G3BPs remains elusive. Given the broad functional involvement of
different domains within G3BPs across various biological processes, it is imperative that future investigations prioritize unraveling the molecular structure of G3BPs to gain insights into their protein interactions at the molecular level. A thorough understanding of G3BPs’ structural features will be critical in the rational design of drugs or inhibitors that can specifically target their protein interactions. This can be used to treat not only cancer patients but also reduce viral infection and neurological diseases.

Author Contributions

Wrote and contributed to the writing of the manuscript: Mukhopadhyay, C. and Zhou, P

References


Galan A, Lozano G, Pineiro D, Martinez-Salas E (2017) G3BP1 interacts directly with the FMDV IRES
and negatively regulates translation. **FEBS J** 284: 3202-3217

A novel phosphorylation-dependent RNase activity of GAP-SH3 binding protein: a potential link
between signal transduction and RNA stability. **Mol Cell Biol** 18: 3956-3965

granule assembly is mediated by prion-like aggregation of TIA-1. **Mol Biol Cell** 15: 5383-5398

microRNA-223 target for regulating the proliferation and invasion of human breast cancer cells.
**Biomed Pharmacother** 67: 629-636

Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, O'Meara MJ, Rezelj VV, Guo JZ,
**Nature**

Separate domains of G3BP promote efficient clustering of alphavirus replication complexes and
recruitment of the translation initiation machinery. **PLoS Pathog** 15: e1007842

Wang J, Mateju D *et al* (2020) RNA-Induced Conformational Switching and Clustering of G3BP Drive
Stress Granule Assembly by Condensation. **Cell** 181: 346-361 e317

tumors and promotes S phase entry. **Cancer Lett** 162: 213-221

Guo YX, Wang N, Wu WC, Li CQ, Chen RH, Zhang Y, Li X (2021) The Role of miR-23b in Cancer
and Autoimmune Disease. **J Oncol** 2021: 6473038

granule-associated protein G3BP2 regulates breast tumor initiation. **Proc Natl Acad Sci U S A** 114:
1033-1038

mediates stress granule disassembly in a context-specific manner. **Science** 372: eabf6548
He M, Yang Z, Abdellatif M, Sayed D (2015) GTPase Activating Protein (Sh3 Domain) Binding Protein 1 Regulates the Processing of MicroRNA-1 during Cardiac Hypertrophy. PLoS One 10: e0145112
Katsafanas GC, Moss B (2004) Vaccinia virus intermediate stage transcription is complemented by Ras-GTPase-activating protein SH3 domain-binding protein (G3BP) and cytoplasmic activation/proliferation-associated protein (p137) individually or as a heterodimer. *J Biol Chem* 279: 52210-52217


Rao SG, Jackson JG (2016) SASP: Tumor Suppressor or Promoter? Yes! *Trends Cancer* 2: 676-687


Sonnhof U, Grafe P, Krumnikl J, Linder M, Schindler L (1975) Inhibitory postsynaptic actions of taurine, GABA and other amino acids on motoneurons of the isolated frog spinal cord. *Brain Res* 100: 327-341


Footnotes

This work was supported in part by R01 CA221152, CTSC (1 UL1 TR002384) Pilot Award and the Weill Cornell Medicine Prostate SPORE’s Developmental Research Award to P.Z. and US Department of Defense (W81XWH-17-1-0176) to C.M. We thank Dr. Sarah See for critical reading and editing of the manuscript and constructive comments and suggestions.

The authors declare that they have no conflict of interest with any company that could benefit from the findings of this manuscript.

Figure Legends

Figure 1. Schematic representation of different domain structure of G3BP1 and G3BP2.

Both G3BP1 and G3BP2 have an NTF2 domain at the N-terminus and an RRM/RGG domain at the C-terminus. However, G3BP1 has only one PxxP domain, while G3BP2a and G3BP2b contain four and five PxxP domains, respectively.

Figure 2. Summary of well-characterized and emerging roles of (a) G3BP1 and (b) G3BP2

(a) Different functions of G3BP1 in cancer, stress granule formation, RNA stabilization, and viral infections. (b) Different functions of G3BP2 in cancer, stress granule formation, and RNA stabilization.
Figure 1
Figure 2

(a) mRNA stability

(b) Cancer

Figure 2