

REVIEW

Open Access



# Interaction between non-coding RNAs, mRNAs and G-quadruplexes

Soudeh Ghafouri-Fard<sup>1</sup>, Atefe Abak<sup>2</sup>, Aria Baniahmad<sup>3</sup>, Bashdar Mahmud Hussen<sup>4,5</sup>, Mohammad Taheri<sup>3\*</sup>, Elena Jamali<sup>6\*</sup> and Marcel E. Dinger<sup>7\*</sup>

## Abstract

G-quadruplexes are secondary helical configurations established between guanine-rich nucleic acids. The structure is seen in the promoter regions of numerous genes under certain situations. Predicted G-quadruplex-forming sequences are distributed across the genome in a non-random way. These structures are formed in telomeric regions of the human genome and oncogenic promoter G-rich regions. Identification of mechanisms of regulation of stability of G-quadruplexes has practical significance for understanding the molecular basis of genetic diseases such as cancer. A number of non-coding RNAs such as H19, XIST, FLJ39051 (GSEC), BC200 (BCYRN1), TERRA, pre-miRNA-1229, pre-miRNA-149 and miR-1587 have been found to contain G-quadruplex-forming regions or affect configuration of these structures in target genes. In the current review, we outline the recent research on the interaction between G-quadruplexes and non-coding RNAs, other RNA transcripts and DNA molecules.

**Keywords:** lncRNA, miRNA, mRNA, G-quadruplex, Expression

## Introduction

G-quadruplexes are secondary helical structures formed as four-stranded nucleic acid structures between guanine (G)-rich nucleic acids. These structures have a helical shape and comprise guanine tetrads that can be made from one [1], two [2] or four molecules [3]. The unimolecular types are usually seen in the telomeric regions, as well as transcriptional regulatory regions [4]. G-quadruplex structures consist of a core G-rich section, including G-tetrads loaded on top of each other and zero or more connecting loops with diverse compositions [5]. The G-rich core classically contains at least two stacked G-tetrads that have a right-handed helical twist. These

stacks are combined together by the normal sugar-phosphate backbone. Hydrogen bonds between the Gs in a plane,  $\pi$ - $\pi$  interactions between the Gs in neighboring surfaces and charge-charge interaction between the partially negative O6 of the G bases and cations provide the binding energy in these structures. Monovalent cations, particularly K<sup>+</sup> have the stabilizing role in these structures. Changes of the bases to non-G bases can destabilize these structures [6].

This structure is seen in the promoter regions of numerous genes under certain conditions. G-quadruplexes are involved in several cellular functions, including DNA replication, gene expression, protection of telomeres, and apoptosis [7–9].

These structures reside in important locations in genomic DNA within both coding and non-coding regions. Through residing in these strategic locations, they can participate in several crucial functions at cellular and organismal levels [10]. Formation of these structures between guanine-rich domains renders these regions thermodynamically stable [11].

\*Correspondence: mohammad.taheri@uni-jena.de; elena.jamali@yahoo.com; m.dinger@unsw.edu.au

<sup>3</sup> Institute of Human Genetics, Jena University Hospital, 07740 Jena, Germany

<sup>6</sup> Skull Base Research Center, Loghman Hakin Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>7</sup> School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, NSW, Australia

Full list of author information is available at the end of the article



These structures are formed by telomeric regions in the human genome and oncogenic promoter G-rich regions [12].

DNA G quadruplex-folded regions have been shown to be associated with alterations in transcriptional activity. A recent study has demonstrated that the presence of these structures in promoters is consistently linked with open chromatin configuration and increased transcription of genes. G quadruplex-folded has binding sites of transcription factors activator protein-1 (AP-1) and specificity protein-1 (Sp1), therefore being associated with determination of cell-specific transcriptional programs [13]. A recent study has suggested a model for understanding the mechanism by which G quadruplexes regulate transcription. This model suggests that G quadruplexes act as transcription suppressors through inhibiting polymerase processivity. A bulk of evidence has recently emerged to support this model. However, there is still a misrepresentation of G quadruplexes as transcriptional barriers. In fact, formation of G quadruplexes can potentially affect gene expression at several diverse levels through functioning as an important regulatory mechanism upsetting the landscape of epigenetic marks and chromatin structure [14]. The interaction between formation or disruption of G-quadruplexes and other epigenetic marks such as DNA and histone modifications, nucleosome positioning, and three-dimensional configuration of chromatin has essential role in regulation of gene expression [10].

Notably, wild-type Telomerase reverse transcriptase (hTERT) promoter sequences do not have the ability to make a hairpin structure in solution, yet they can fold into a compact arranged three-G-quadruplex configuration [15]. A number of cancer-related mutations have been shown to destabilize hTERT promoter G-quadruplexes and induce defects in telomere-repeat-binding-factor 2 (TRF2) binding. Notably, ligand-induced stabilization of G-quadruplexes could restore TRF2 binding and hTERT re-inhibition. Cumulatively, these structures are associated with regulation of hTERT activity [16]. Another study has shown that the basic N-terminal Gly/Arg-rich (GAR) domain of TRF2 can bind Telomere-repeat-encoding RNA (TERRA). In fact, disruption of the TERRA-TRF2 GAR complex by small molecules or defects in the GAR domain of TRF2 leads to defects in TERRA, and activation of  $\gamma$ H2AX-related DNA damage in telomeres. This could result in reduced telomere length, and induction of telomere abnormalities such as fragility of telomeres. Cumulatively, G-quadruplex structure of TERRA can recognize element for TRF2 GAR domain. Interaction between TRF2 GAR and TERRA has a crucial role in the maintenance of telomere stability [17].

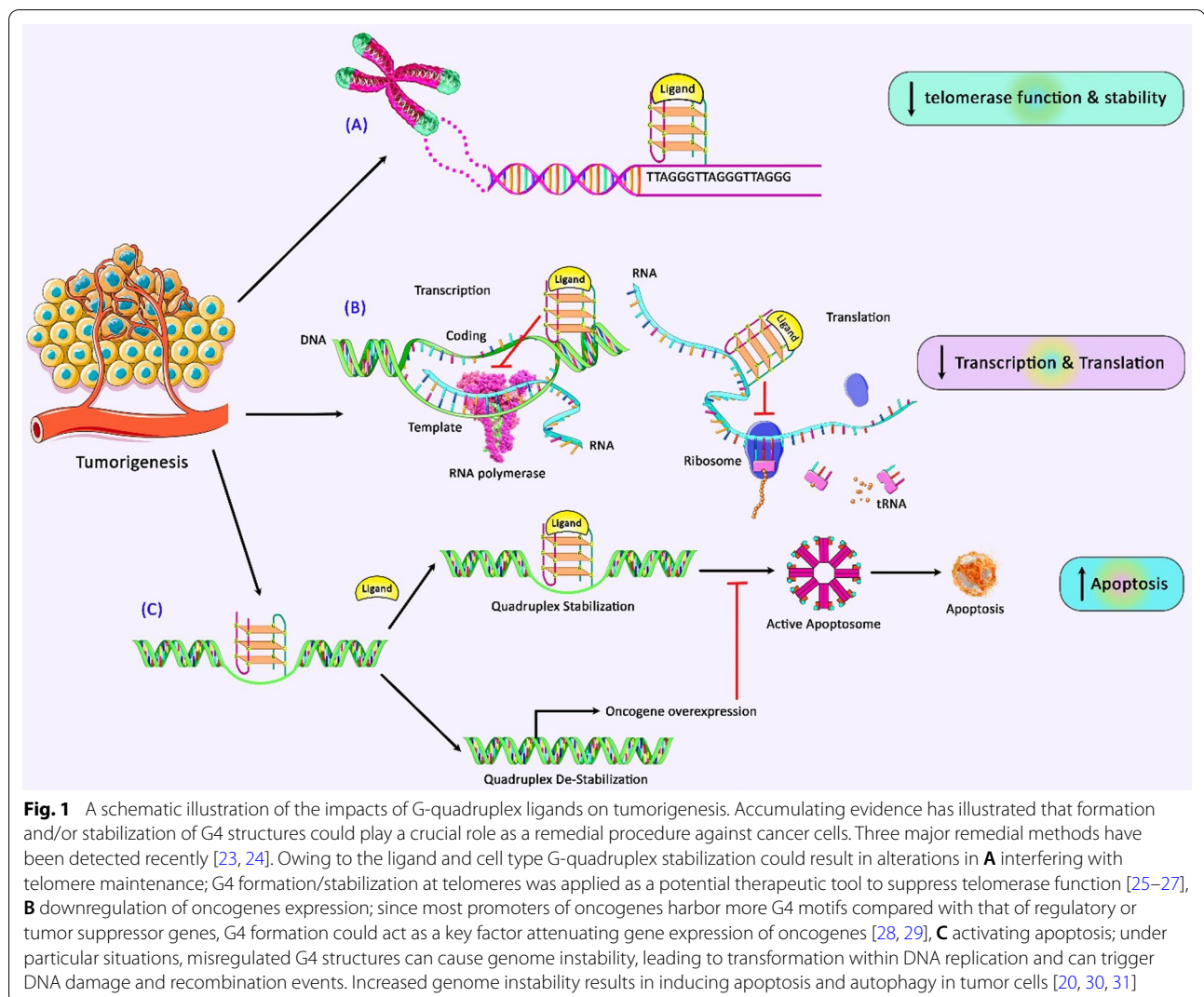
Zheng et al. have shown that an artificial protein can bind G-quadruplexes with high affinity and specificity. This protein has been used to capture G-quadruplexes in living cells from different species, providing the detailed landscape of these structures. This study has shown association between transcription and an extensive construction of G-quadruplexes in genes [18]. Another study has shown direct binding of Yin Yang-1 (YY1) to G-quadruplex structures. Moreover, YY1 binding sites have been shown to have extensive overlap with G-quadruplex structure loci in chromatin. In addition, YY1-mediated long-range DNA looping depends on its dimerization and takes place via its recognition of G-quadruplexes [19].

Predicted G-quadruplex-forming sequences are distributed across the genome in a non-random manner. Approximately half of the genes in the human genome are predicted to produce G-quadruplexes near their promoter regions. Many of these structures are present in the vicinity of oncogene promoters or regulatory genes [20]. The transcriptionally active single-stranded form, double-stranded form, and G-quadruplex structures of the promoter are in a delicate balance. Therefore, it is possible to inhibit expression of genes through stabilizing the G-quadruplex structure. Thus, a number of therapeutic strategies have been designed to stabilize secondary DNA structures that are present in the promoter regions of oncogenes. Since stabilization of G-quadruplexes is a possible modality for cancer therapy [21], identification of mechanisms of regulation of stability of G-quadruplexes has practical significance (Fig. 1). In the current review, we outline the recent insights about the presence of G-quadruplexes in non-coding RNAs, other transcripts and DNA molecules.

The G-quadruplex structure within pre-miRNA-149 has been demonstrated to suppress activity of Dicer, therefore decreasing maturation of miRNA-149 in neoplastic cells. Moreover, the inhibitory role of miR-149 on cell proliferation can be achieved through interfering with the G-quadruplex structures existing in the pre-miRNA-149. TmPyP4 (5,10,15,20-Tetrakis-(*N*-methyl-4-pyridyl)porphine) is widely used as a photosensitizer and a modulator of nucleic acid secondary structure with an inhibitory effect on G-quadruplex formation could increase levels of miR-149 in breast cancer cells, leading to reduction of Zinc Finger And BTB Domain Containing 2 (ZBTB2) expression and attenuation of cell proliferation [22].

### Detection of G-quadruplexes in cells and in vitro

Identification of G-quadruplex structures in cells can be accomplished using modified antibodies, G-quadruplex based aptamers as well as small molecules [32].



G-quadruplexes can be detected in chemically fixed human cells using specific antibodies. Previous studies have used immunostaining [33] or immunoprecipitation [34] techniques for this purpose. In these techniques, antibodies against G-quadruplexes bind with these structures in a non-native cellular setting following some treatments. However, these treatment steps might affect construction of G-quadruplex. It has been demonstrated that treatment with RNase H can remove G-quadruplex in the non-transcribed strand of R-loop [35]. Therefore, identification of G-quadruplexes in living cells is a preferred method. Since antibodies cannot permeate into cells, it is not possible to use them for living cells. Moreover, cytoplasm has a reducing environment which interferes with construction of the disulfide bonds needed for preserving the tertiary structure of antibodies [36]. Zheng et al. have reported an artificial G-quadruplex

probe protein which specifically binds G-quadruplex with high affinity. Application of this probe in living cells has led to identification of genome-wide landscape of G-quadruplexes [37].

### Non-coding RNAs and G-quadruplexes

Both long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) have been found to contain G-rich regions predicted to form G-quadruplexes. For instance, *NEAT1* contains such regions. *NEAT1* functions as a platform for the assembly of paraspeckles, which are a type of organelle within the nucleus participating in the regulation of gene expression. Assembly of paraspeckles requires *NEAT1*-mediated recruitment of the RNA-binding protein NONO. NONO has been found to bind with the G-quadruplex structure of G-rich C9orf72 repeat RNA. *NEAT1* contains several G-quadruplex motifs.

Furthermore, NONO can bind with *NEAT1* G-quadruplexes in a specific manner suggesting that G-quadruplex motifs may facilitate interaction between NONO and *NEAT1*. Notably, NONO binding sites on *NEAT1* mainly correspond to G-quadruplex motifs. Consistent with this finding, disruption of G-quadruplexes with specific small molecules leads to separation of intuitive NONO-*NEAT1* complexes. Therefore, G-quadruplexes have been suggested as principal candidates for the NONO-recruiting components of *NEAT1* [38].

Another study has reported the presence of an evolutionarily conserved G-rich region at the 5' end of the *H19* coding gene which is predicted to form a G-quadruplex structure. Further assays with G-quadruplex-specific ligands have shown the ability of the G-rich motif adjacent to the transcription start site in constructing a G-quadruplex. Most notably, this G-quadruplex has been found to regulate expression of the *H19* gene. Sp1 and E2F1 are two transcription factors that interact with this G-quadruplex to either inhibit or enhance transcription of *H19*, respectively. In addition, expression of *H19* in the course of differentiation of mice embryonic stem cells seems to be controlled by a G-quadruplex structure in this lncRNA [39].

Telomeric Repeat-containing RNA (TERRA), which is transcribed from telomeres, has been shown to contain G-quadruplex structures. Notably, unstructured hinge domains that participate in the targeting of HP1 $\alpha$  to constitutive heterochromatin regions recognize these structures of TERRA. Through this mechanism, TERRA contributes to the enrichment of HP1 $\alpha$  at telomeric regions to preserve the heterochromatin structure. Additionally, HP1 $\alpha$  has been shown to bind more quickly to G-quadruplex structures having parallel topology versus those with antiparallel topology. These G-quadruplex structures have been seen in the regulatory portions of numerous oncogenes. Therefore, such non-canonical configurations have been determined as regulators of HP1 $\alpha$  function and chromatin domain structure participating in the epigenetic regulation of gene expression [40].

In an attempt to assess the expression profile of colon cancer samples, Matsumura et al. have identified a novel up-regulated lncRNA in colon cancer tissues, namely FLJ39051 or GSEC (G-quadruplex-forming sequence containing lncRNA). Inhibition of GSEC lncRNA transcription resulted in a significant decrease in the motility of cancer cells. This lncRNA was shown to bind to the DHX36 RNA helicase through its G-quadruplex-forming sequence and suppress the DHX36 G-quadruplex unwinding function. Thus, GSEC is thought to participate in the migration of colon cancer cells through suppression of activity of DHX36 through its G-quadruplex

configuration [41]. Interestingly, G-quadruplex structures are conserved in L1 sub-families and may therefore result in an increased level of retro-transposition activity [42].

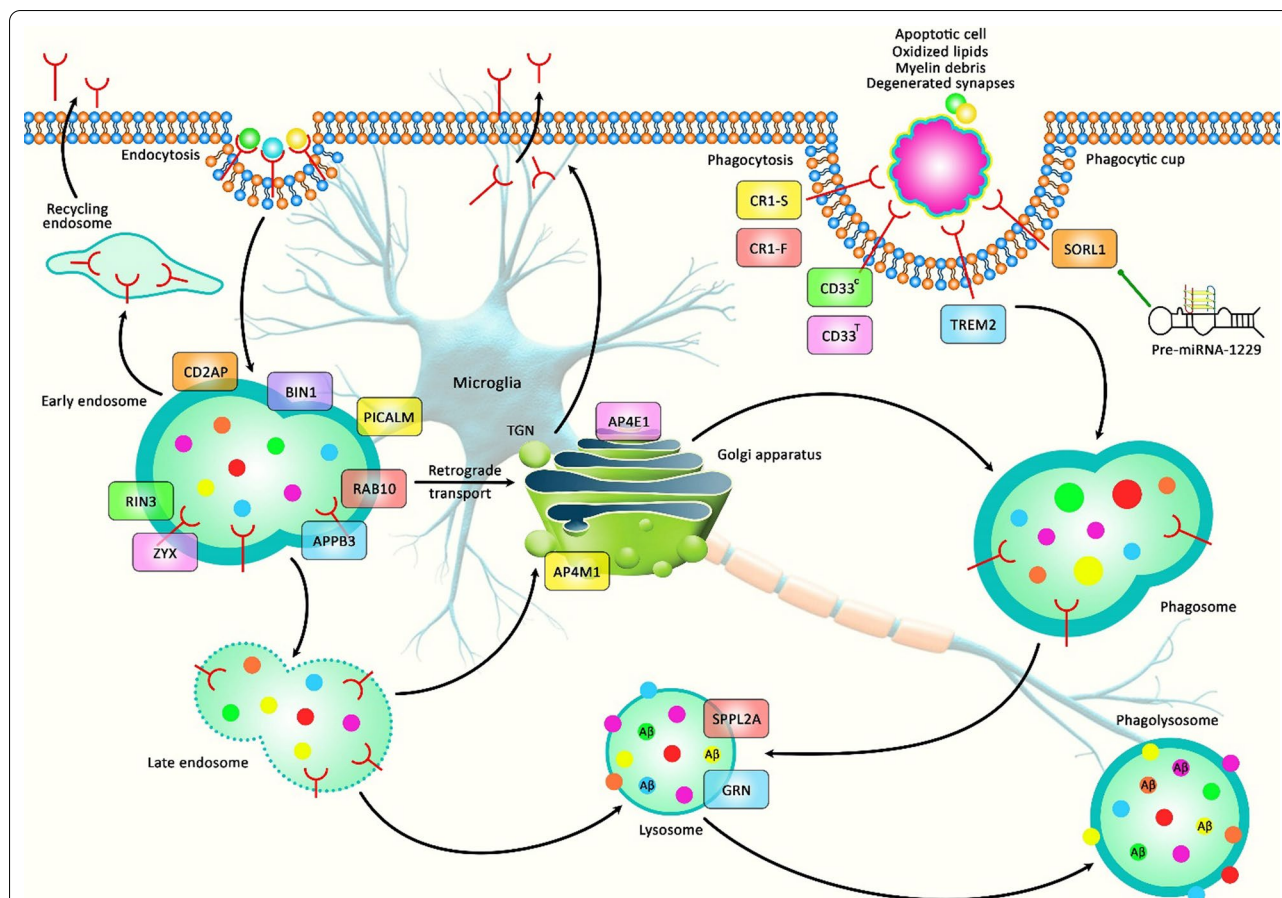
In addition to these G-quadruplex-containing lncRNAs, some lncRNAs have been found to alter expression of genes by affecting G-quadruplex structures in target genes. lncRNA *XIST* has been found to be processed into a small transcript called XPI2. This small transcript has a gender-independent expression pattern, implying that it has a role outside of X-chromosome inactivation. Nucleolin and hnRNP A1 are two XPI2-related proteins that are functionally associated with G-quadruplex structures. XPI2 silencing has decreased the activity of the KRAS pathway. Further studies have supported the interaction between XPI2 and the polypurine-polypyrimidine regions of KRAS. Therefore, XPI2 might induce expression of KRAS by decreasing G-quadruplex formation. Thus, it suggests that XPI2 has a role in KRAS-associated tumorigenesis through regulation of G-quadruplex structures [43].

A further group of lncRNAs has neither G-quadruplex structures nor directly regulate expression of target genes through affecting stability of these structures, but instead have interactions with ATP-dependent RNA helicases such as RHAU that exhibit high affinity for G-quadruplex structures. An example of these lncRNAs is *BC200*. This lncRNA does neither form G-quadruplex structures nor interact with the quadruplex-interacting region of RHAU, but it directly binds to RHAU. *BC200* acts as an acceptor of unwound quadruplexes through a cytosine-rich area in the vicinity of the 3'-end of this transcript. *BC200* has an interaction with the G-quadruplex-containing telomerase RNA. Therefore, RHAU might facilitate *BC200* binding and consequent regulatory effects with G-quadruplex-harboring nucleic acid regions [44].

Importantly, G-quadruplexes within premature microRNA precursors (pre-miRNAs) might also affect risk of human disorders. For instance, pre-miRNA-1229 has been shown to contain a variant that is associated with risk of Alzheimer's disease. The mature form of this miRNA modulates translation of SORL1. Pre-miRNA-1229 forms a G-quadruplex configuration that co-occurs in a balanced state with the canonical hairpin structures, possibly regulating levels of miR-1229-3p. Most notably, the Alzheimer's disease-associated variant of pre-miR-1229 appears to alter the balance between these structures. Consequently, this G-quadruplex structure has been suggested as a putative therapeutic target for Alzheimer's disease [45] (Fig. 2).

The G-quadruplex structure within pre-miRNA-149 has been demonstrated to suppress activity of Dicer, therefore decreasing maturation of miRNA-149 in





**Fig. 2** A schematic representation of the interaction between G-quadruplex structure of pre-miRNA-1229 and endolysosomal processing in microglial cells in Alzheimer’s disease. Previous studies have authenticated that SORL1 could play an effective role in binding Aβ and facilitating its degradation in the lysosomes [46]. As an illustration, recent study has detected that Pre-miRNA-1229 rs2291418 variant, which is significantly associated with Alzheimer’s diseases, alters its structure to the extended hairpin structure and enhances SORL1 transcription. SORL1 is a protein that is responsible for the processing and trafficking of Aβ in AD [45]

neoplastic cells. Moreover, the inhibitory role of miR-149 on cell proliferation can be achieved through interfering with the G-quadruplex structures existing in the pre-miRNA-149. TmPyP4 with an inhibitory effect on G-quadruplex formation could increase levels of miR-149 in breast cancer cells, leading to reduction of ZBTB2 expression and attenuation of cell proliferation [22].

In a separate example involving G-quadruplexes and miRNAs, miR-1587 has been shown to contain a G-rich region forming stable G-quadruplex structure in certain conditions described by the presence of potassium and sodium ions and low levels of ammonium cation. High levels of ammonium cation or molecular crowding milieus have been shown to induce a dimeric G-quadruplex in miR-1587 via 3'-to-3' assembling of two monomeric G-quadruplex units with one ammonium ion confined between the edges. Notably, two manufactured jatrorrhizine products have been shown to trigger

the dimerization of miR-1587 G-quadruplexes. On the other hand, jatrorrhizine could not induce this structure in spite of its ability to bind with the dimeric miR-1587 G-quadruplexes [47].

Table 1 shows the list of noncoding RNAs which have G-quadruplexes or regulate expression of genes through modulation of these structures.

**Protein coding transcripts and G-quadruplexes**

G-quadruplexes structures are enriched in 3' UTRs of mRNAs, where miRNAs could also bind. G-quadruplex structures have been shown to affect miRNA binding to target mRNAs, providing a new mechanism for G-quadruplex-dependent modulation of miRNA-mRNA interactions that have fundamental roles in the maintenance of gene expression [51]. FMRP binding with the G-rich region of the PSD-95 transcript provides an important example of the interference of G-quadruplexes

**Table 1** The presence and function of G-quadruplexes in non-coding RNAs

Non-coding RNAs	Location	Ligands	Cell line	Clinical samples/animal models	References
<i>NEAT1</i>	–	NONO	HEK293T	–	[38]
<i>H19</i>	5' end	Sp1, E2F1	HEK293T, HeLa, U2OS, EpH4, mESCs	–	[39]
<i>XIST</i>	–	Nucleolin, hnRNP A1, KRAS	Huh-7, MCF-7, normal lymphoid cells	31 colon cancer tissues and their adjacent non-tumorous tissues	[43]
<i>FLJ39051 (GSEC)</i>	–	DHX36	DLD-1, SW480	105 samples of colon Carcinoma tissues and normal colon samples	[41]
<i>BC200 (BCYRN1)</i>	–	RHAU	HEK293T, HeLa, MCF-7, T47D, MDA-MB-231, SK-BR-3, A549	–	[44]
<i>TERRA</i>	–	HP1 $\alpha$	NIH3T3	–	[40]
<i>pre-miRNA-1229</i>	–	SORL1	–	–	[45]
<i>pre-miRNA-149</i>	–	ZBTB2, Porphyrin	MCF-7	–	[22]
<i>miR-1587</i>	3'-UTR	TAGLN, pseudopalmitine, TMPyP4	HeLa	–	[47]
<i>pre-miRNA 92b</i>	–	LNA	A549 cells, NSCLC	–	[48]
<i>LINE-1</i>	3'-UTR	–	HeLa	–	[42]
<i>miR-3620-5p</i>	5' and 3' ends	Sanguinarine	–	–	[49]
<i>pre-let-7</i>	–	Lin28	Human NCCIT embryonal carcinoma cells	–	[50]

with miRNA-mRNA interactions. Notably, 3' UTR of PSD-95 transcript has a miR-125a binding site which is located in a G-rich region bound by FMRP. FMRP regulates expression of PSD-95 through phosphorylation-related mechanisms. Both unphosphorylated FMRP and its phosphomimic FMRP S500D have a high affinity for binding with G-quadruplexes within PSD-95 transcript. However, only FMRP S500D can bind with to miR-125a. Therefore, FMRP functions as a molecular switch to regulate stability of the complex constructed between the miR-125a-RISC and PSD-95 transcript in a phosphorylation-dependent manner [52].

G-quadruplexes have also been found to form within other regions of mRNAs. For instance, a G-quadruplex structure has been found within the 5' UTR of the potassium 2-pore domain leak channel *Task3* transcript. The stability of this structure has been preserved under physiological ionic concentrations. Such structures can inhibit translation of *Task3*. A G-quadruplex-specific helicase, namely DHX36 can intervene with this structure resulting in as increase in K<sup>+</sup> leak flow and induction of membranes hyperpolarization. The G-quadruplex structure has an essential role in transport of *Task3* transcripts to distal primary cortical neurites. Since abnormal *Task3* levels have been correlated with abnormal function of neurons, the role of this G-quadruplex in the regulation of K<sup>+</sup> leak within neurons shows the importance of this route in the pathogenesis of neurological disorders [53].

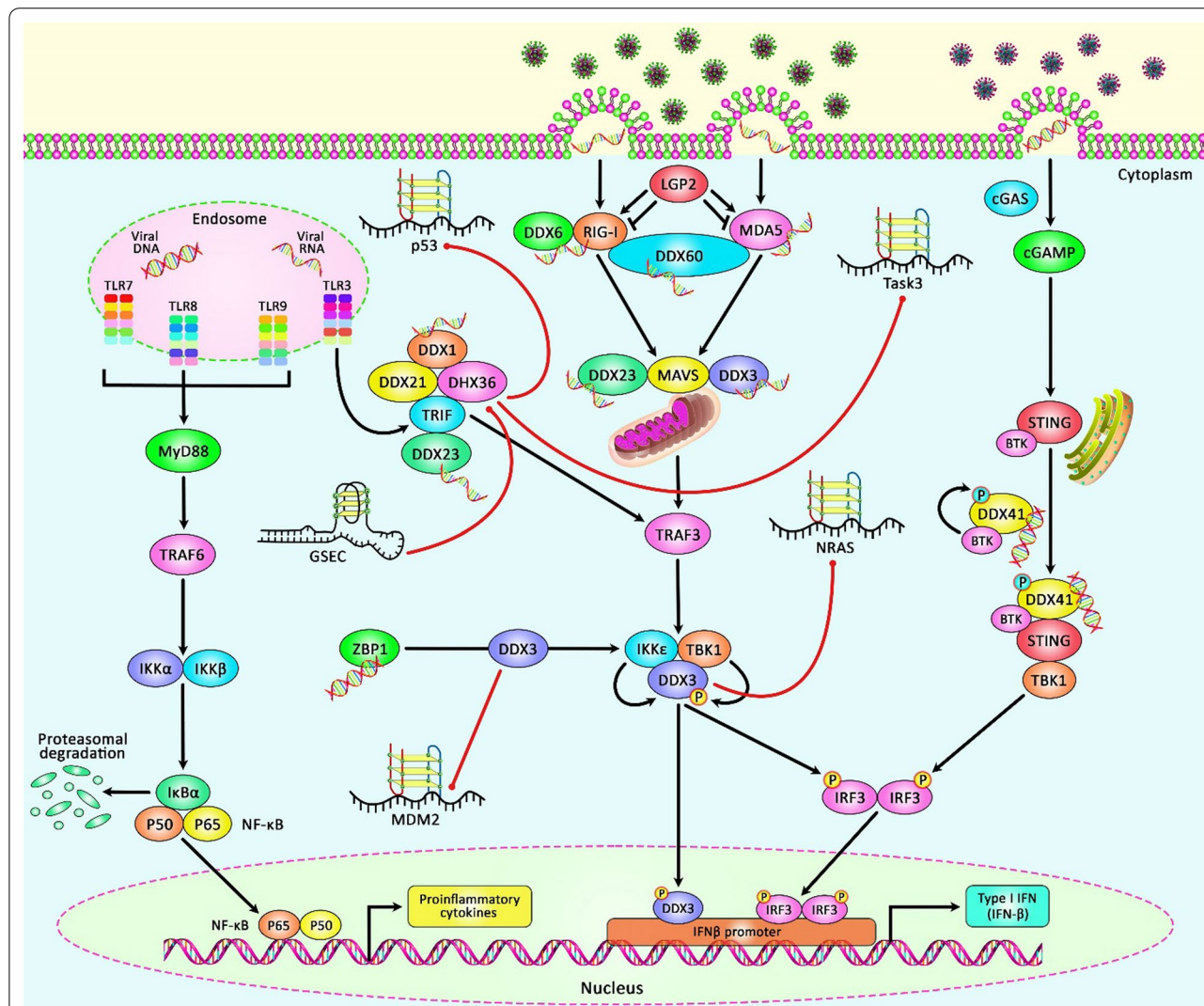
*BAG-1* is another gene that contains a G-rich region in its 5'UTR capable of forming a G-quadruplex structure. This structure has been found to regulate cap-dependent as well as cap-independent expression of *BAG-1*. SNRPA has been demonstrated to bind directly to the *BAG-1* transcript via these G-quadruplexes modulating expression of the *BAG-1* gene [54].

Another study has shown that translation of *NRXN2 $\alpha$*  is regulated by a G-quadruplex structure in its 5' UTR. The 5' UTR of this gene has an inhibitory effect on its expression. Notably, there is a crucial subregion in this area that accounts for the main inhibitory effect through formation of a certain secondary G-quadruplex configuration. In addition, the upstream AUGs work in a synergistic mode with G-quadruplex to inhibit *NRXN2 $\alpha$* -expression. Therefore, the 5' UTR of *NRXN2 $\alpha$*  suppresses its translation through different mechanisms [55].

In spite of the observed inhibitory effect of G-quadruplexes in the 5' UTR of genes on their expression [55], two G-quadruplex structures in the 5' UTR of *TGF $\beta$ 2* mRNA have been shown to increase its expression. These structures are thought to work additively to noticeably upregulate *TGF $\beta$ 2* expression [56]. Consistent with this study, is the enhanced expression of an isoform of *ARC2* through the presence of a G-quadruplex structure in the longer variant of the 5' UTR of the *ARPC2* transcript. This variant of the 5' UTR also has an internal ribosome entry site (IRES). This variant of

5' UTR has been shown to promote cap-independent translation of *ARPC2*. The G-quadruplex also contributes to the activity of IRES. Consistent with the supposed role of IRES in induction of expression of genes under cellular stress through cap-dependent translation, expression of *ARPC2* has been shown to be increased at high cell density. Therefore, it is proposed

that a mechanistic model of IRES upregulation is underpinned by the G-quadruplex motif exposed from the chief stem-loop component [57]. Figure 3 demonstrates the interaction between lncRNA, mRNAs and G-quadruplexes in the regulation of DEAD-box helicases in antiviral innate immunity signaling pathways (Table 2).



**Fig. 3** A schematic diagram of the interaction between lncRNA, mRNAs and G-quadruplexes in modulating DEAD-box helicases in antiviral innate immunity signaling cascades. DEAD-box helicases have been detected to have a significant role as sensors for nucleic acids, containing dsRNA, cytoplasmic DNA, and viral RNAs, resulting in triggering the induction of interferon and interferon-stimulated genes. Besides, DEAD-box helicases could involve in innate immune cascade downstream of nucleic acid-sensing via modulating protein-protein interactions and elevating the DAMP cascade [48–50]. Previous studies have authenticated the interaction between ncRNAs, mRNAs and G-quadruplexes regulating DEAD-box helicases members containing DDX3 and DHX36. As an illustration, accumulating finding has suggested that lncRNA GSEC could play a crucial role in colon cancer cell migration via suppressing the function of DHX36 through its G-quadruplex structure. In fact, GSEC could bind to DHX36 RNA helicase via its G-quadruplex-forming sequence, thereby attenuating DHX36 G-quadruplex unwinding activity [9]. In addition, another research has demonstrated that DHX36 could bind to the p53 RNA G4-forming sequence, whilst a mutation in the p53 G4 sequence could result in suppressing the DHX36 function to process its pre-mRNA 3'-end [34]. All the information regarding the presence and function of G-quadruplexes in ncRNAs and mRNA coding genes can be seen in Tables 1 and 2.

**Table 2** The presence and function of G-quadruplexes in mRNA coding genes

Protein-coding genes	Location	Ligands	Cell line	Clinical samples/animal models	References
<i>Task3</i>	5'-UTR	DHX36	HEK293	C57Bl/6 wild-type mice	[53]
<i>BAG-1</i>	5'-UTR	SNRPA	HCT-116	–	[54]
<i>NRXN2a</i>	5'-UTR	–	SH-SY5Y, SK-N-SH, U87MG, HEK293	–	[55]
<i>TGFβ2</i>	5'-UTR	–	MCF-7	–	[56]
<i>ARPC2</i>	5'-UTR	–	HEK293, MCF7	–	[57]
<i>KNCJ11</i>	3'-UTR	miR-331-3p, TMPyP4	HEK-293A	Cardiomyocytes isolated from newborn SD rats	[51]
<i>PSD-95</i>	3'-UTR	FMRP, miR-125a	–	–	[52]
<i>NRAS</i>	5'-UTR	ZnAPC	MCF-7	–	[58]
	5'-UTR	–	DDX3X, DDX5, DDX17, GRSF1, NSUN5	HeLa, Flp-In T-REx 293	[59]
<i>Hnf4a1</i>	5'-UTR	–	HEK293T, HepG2-C3A	–	[60]
<i>Bcl-2</i>	5'-UTR	–	HEK293, A-375	–	[61]
<i>SMNDC1</i>	5'-UTR	FMRP	–	E17 mouse brain lysate	[62]
<i>FADS2</i>	3'-UTR	mir331-3p	HEK293, Huh7, HCT116	–	[63]
<i>PITX1</i>	3'-UTR	RHAU	–	–	[64]
<i>p53</i>	3'-end	DHX36	A549, HCT116 WT, p53 KO cells	–	[65]
<i>SNCA</i>	5'-UTR	–	HEK-293, SK-N-SH, Neuro-2a	–	[66]
<i>NRF2</i>	5'-UTR	EF1a	HEK293, HeLa	–	[67]
<i>ADAM10</i>	5'-UTR	A methyl-quinolinium derivative	HeLa, HEK-APP	–	[68]
<i>VEGF</i>	5'-UTR	360A, Phen-DC	HeLa	–	[69]
<i>NR2B</i>	3'-UTR	FMRP	–	E17 mouse brain lysate	[70]
<i>Nkx2-5</i>	5'-UTR	RHAU	H9C2, 293T, COS7, E14.5 cardiomyocytes	Rhau conditional KO mice	[71]
<i>APP</i>	3'-UTR	–	HeLa, HEK293	–	[72]
<i>Gap-43</i>	5'-UTR	hnRNP-Q1	N2a cells	Timed pregnant C57BL/6J mice	[73]
<i>MDM2</i>	Adjacent to an E-box DNA motif	ACBL, hnRNP family, XRCC6, XRCC5, DDX3X, EWS, Ku70-Ku80 protein dimer	93T449, HNLf, WDLPS	–	[74]
<i>PIM1</i>	–	–	–	–	[75]
<i>c-MYC</i>	Promoter	A quinoxaline analog: 6,7-Difluoro-2,3-bis(4-(4-methylpiperazin-1-yl)phenyl) quinoxaline (QN-1)	4T1 cells	Female BALB/c mice	[76]
<i>HOXC10</i>	–	CHD7	HeLa, MDA-MB-231	–	[77]
<i>CD44</i>	Splicing cis element	hnRNPF	HMLE, HMLE-Twist-ER, MCF10A, HEK293	–	[78]

## Discussion

Several lncRNAs and mRNA coding genes have been found to contain G-quadruplexes or regulate expression of genes through modulation of these structures. G-quadruplexes have prominent roles in the regulation of gene expression and interventions with these structures are emerging as novel therapeutic opportunities in genetic diseases such as cancer. Therefore, identification

of lncRNAs/mRNAs that modulate G-quadruplexes is important.

G-quadruplexes are also being discovered in miRNA precursors suggesting a role for RNA G-quadruplexes in the regulation of miRNA biogenesis and control of interaction of non-coding RNAs with their partners [79].

Notably, numerous identified G-quadruplexes in non-coding RNAs has been shown to be unstable, being



detected only in the presence of certain ligands or ions [79]. Moreover, G-quadruplexes in pri-miRNAs and pre-miRNAs are present in a well-regulated balance with the hairpin structure. This balance can permit appropriate regulation of gene expression [79].

Secondary structures formed within non-coding RNAs can determine their mode of action and their effect on targets of these transcripts. Notably, the G-quadruplex structures within precursor miRNAs can affect the structure of hairpin stem loops that have essential roles in recognition of these structures by Dicer recognition and additional maturation steps [22]. The importance of this finding is further highlighted by the observation that approximately 16% of identified human pre-miRNAs can embrace G-quadruplex structures instead of acknowledged stem-loops [80]. Consistently, a number of studies have suggested stimulation of G-quadruplex development and dimerization as a new approach for regulation of functions of certain miRNAs [47]. Meanwhile, G-quadruplex structures exist in the 3' UTR of mRNAs, a region which is targeted by miRNAs. Therefore, G-quadruplexes can affect miRNA-mRNA interactions.

Among G-quadruplex-containing lncRNAs are those with significant roles in carcinogenesis, such as *NEAT1*, *H19* and *GSEC*, providing additional evidence for association between these structures and malignant transformation of cells. In addition, G-quadruplexes within non-coding RNAs might affect the pathogenesis of neurologic disorders such as Alzheimer's disease [45].

## Conclusions

Taken together, we have summarized evidence for prevalent presence of G-quadruplex structures in both miRNAs and lncRNAs and association between construction of these structures within pri- and pre-miRNAs and miRNA synthesis. Moreover, G-quadruplexes have been found to affect binding of miRNAs and lncRNAs with their target transcripts and interacting proteins, respectively.

G-quadruplexes represent novel targets for therapeutic interventions. As some transcripts can alter these structures, manipulation of expression of these transcripts is a possible therapeutic option in this regard. Meanwhile, G-quadruplex structures have been found in several disease-associated lncRNAs and miRNAs. Thus, alteration in the stability of G-quadruplexes within these transcripts is a possible mechanism for dysregulation of these transcripts in human disorders, such as cancer and other genetic diseases.

Since the presence of these structures in RNA molecules might participate in the mechanisms that pathogenic organisms or tumors exploit to evade the hosts' immune responses, future research in this field would

pave the way for identification of novel strategies to combat these two kinds of disorders.

## Acknowledgements

Not applicable.

## Author contributions

SGF and MED wrote the draft and revised it. MT and EJ designed and supervised the study. AB, AA and BMH collected the data and designed the tables and figures. All the authors read and approved the final manuscript.

## Funding

Open Access funding enabled and organized by Projekt DEAL. Not applicable.

## Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent of publication

Not applicable.

### Competing interests

The authors declare they have no competing interests.

## Author details

<sup>1</sup>Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. <sup>2</sup>Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. <sup>3</sup>Institute of Human Genetics, Jena University Hospital, 07740 Jena, Germany. <sup>4</sup>Department of Pharmacognosy, College of Pharmacy, Hawler Medical University, Erbil, Kurdistan Region, Iraq. <sup>5</sup>Center of Research and Strategic Studies, Lebanese French University, Erbil, Kurdistan Region, Iraq. <sup>6</sup>Skull Base Research Center, Loghman Hakin Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. <sup>7</sup>School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, NSW, Australia.

Received: 31 January 2022 Accepted: 19 April 2022

Published online: 29 April 2022

## References

- Largy E, Mergny JL, Gabelica V. Role of alkali metal ions in G-quadruplex nucleic acid structure and stability. *Metal Ions Life Sci.* 2016;16:203–58 (**Epub 2016/02/11. eng**).
- Sundquist WI, Klug A. Telomeric DNA dimerizes by formation of guanine tetrads between hairpin loops. *Nature.* 1989;342(6251):825–9 (**Epub 1989/12/14. eng**).
- Sen D, Gilbert W. Formation of parallel four-stranded complexes by guanine-rich motifs in DNA and its implications for meiosis. *Nature.* 1988;334(6180):364–6 (**Epub 1988/07/28. eng**).
- Verma A, Halder K, Halder R, Yadav VK, Rawal P, Thakur RK, et al. Genome-wide computational and expression analyses reveal G-quadruplex DNA motifs as conserved cis-regulatory elements in human and related species. *J Med Chem.* 2008;51(18):5641–9 (**Epub 2008/09/05. eng**).
- Huppert JL. Structure, location and interactions of G-quadruplexes. *FEBS J.* 2010;277(17):3452–8.
- Gros J, Rosu F, Amrane S, De Cian A, Gabelica V, Lacroix L, et al. Guanines are a quartet's best friend: impact of base substitutions on the kinetics and stability of tetramolecular quadruplexes. *Nucleic Acids Res.* 2007;35(9):3064–75 (**Epub 2007/04/25. eng**).
- Eddy J, Maizels N. Gene function correlates with potential for G4 DNA formation in the human genome. *Nucleic Acids Res.* 2006;34(14):3887–96.

8. Tian T, Chen Y-Q, Wang S-R, Zhou X. G-Quadruplex: a regulator of gene expression and its chemical targeting. *Chem*. 2018;4(6):1314–44.
9. Riou J, Guittat L, Mailliet P, Laoui A, Renou E, Petitgenet O, et al. Cell senescence and telomere shortening induced by a new series of specific G-quadruplex DNA ligands. *Proc Natl Acad Sci*. 2002;99(5):2672–3677.
10. Reina C, Cavalieri V. Epigenetic modulation of chromatin states and gene expression by G-quadruplex structures. *Int J Mol Sci*. 2020;21(11):4172 (**Epub 2020/06/18. eng**).
11. Rhodes D, Lipps HJ. G-quadruplexes and their regulatory roles in biology. *Nucleic Acids Res*. 2015;43(18):8627–37.
12. Patel DJ, Phan AT, Kuryaviv V. Human telomere, oncogenic promoter and 5'-UTR G-quadruplexes: diverse higher order DNA and RNA targets for cancer therapeutics. *Nucleic Acids Res*. 2007;35(22):7429–55.
13. Lago S, Nadai M, Cernilogar FM, Kazerani M, Moreno HD, Schotta G, et al. Promoter G-quadruplexes and transcription factors cooperate to shape the cell type-specific transcriptome. *Nat Commun*. 2021;12(1):1–13.
14. Robinson J, Raguseo F, Nuccio SP, Liano D, Di Antonio M. DNA G-quadruplex structures: more than simple roadblocks to transcription? *Nucleic Acids Res*. 2021;49(15):8419–31.
15. Monsen RC, DeLeeuw L, Dean WL, Gray RD, Sabo TM, Chakravarthy S, et al. The hTERT core promoter forms three parallel G-quadruplexes. *Nucleic Acids Res*. 2020;48(10):5720–34.
16. Sharma S, Mukherjee AK, Roy SS, Bagri S, Lier S, Verma M, et al. Human telomerase is directly regulated by non-telomeric TRF2-G-quadruplex interaction. *Cell Rep*. 2021;35(7):109154.
17. Mei Y, Deng Z, Vladimirova O, Gulve N, Johnson FB, Drosopoulos WC, et al. TERRA G-quadruplex RNA interaction with TRF2 GAR domain is required for telomere integrity. *Sci Rep*. 2021;11(1):1–14.
18. Zheng K-W, Zhang J-Y, He Y-D, Gong J-Y, Wen C-J, Chen J-N, et al. Detection of genomic G-quadruplexes in living cells using a small artificial protein. *Nucleic Acids Res*. 2020;48(20):11706–20.
19. Li L, Williams P, Ren W, Wang MY, Gao Z, Miao W, et al. YY1 interacts with guanine quadruplexes to regulate DNA looping and gene expression. *Nat Chem Biol*. 2021;17(2):161–8.
20. Bochman ML, Paeschke K, Zakian VA. DNA secondary structures: stability and function of G-quadruplex structures. *Nat Rev Genet*. 2012;13(11):770–80.
21. Awadasseid A, Ma X, Wu Y, Zhang W. G-quadruplex stabilization via small-molecules as a potential anti-cancer strategy. *Biomed Pharmacother*. 2021;139:111550.
22. Ghosh A, Ekka MK, Tawani A, Kumar A, Chakraborty D, Maiti S. Restoration of miRNA-149 expression by TmPyP4 induced unfolding of quadruplex within its precursor. *Biochemistry*. 2018;58(6):514–25.
23. Ruggiero E, Richter SN. G-quadruplexes and G-quadruplex ligands: targets and tools in antiviral therapy. *Nucleic Acids Res*. 2018;46(7):3270–83.
24. Cimino-Reale G, Zaffaroni N, Folini M. Emerging role of G-quadruplex DNA as target in anticancer therapy. *Curr Pharm Des*. 2016;22(44):6612–24.
25. Zahler AM, Williamson JR, Cech TR, Prescott DM. Inhibition of telomerase by G-quartet DMA structures. *Nature*. 1991;350(6320):718–20.
26. Kosiol N, Juranek S, Brossart P, Heine A, Paeschke K. G-quadruplexes: a promising target for cancer therapy. *Mol Cancer*. 2021;20(1):1–18.
27. Paudel BP, Moye AL, Abou Assi H, El-Khoury R, Cohen SB, Holien JK, et al. A mechanism for the extension and unfolding of parallel telomeric G-quadruplexes by human telomerase at single-molecule resolution. *Elife*. 2020;9:e56428.
28. Balasubramanian S, Hurley LH, Neidle S. Targeting G-quadruplexes in gene promoters: a novel anticancer strategy? *Nat Rev Drug Discov*. 2011;10(4):261–75.
29. De S, Michor F. DNA secondary structures and epigenetic determinants of cancer genome evolution. *Nat Struct Mol Biol*. 2011;18(8):950–5.
30. Banerjee N, Panda S, Chatterjee S. Frontiers in G-quadruplex therapeutics in cancer: selection of small molecules, peptides and aptamers. *Chem Biol Drug Des*. 2021;99:1–31.
31. Lerner LK, Sale JE. Replication of G quadruplex DNA. *Genes*. 2019;10(2):95.
32. Di Antonio M, Rodriguez R, Balasubramanian S. Experimental approaches to identify cellular G-quadruplex structures and functions. *Methods*. 2012;57(1):84–92 (**Epub 02/11. eng**).
33. Biffi G, Di Antonio M, Tannahill D, Balasubramanian S. Visualization and selective chemical targeting of RNA G-quadruplex structures in the cytoplasm of human cells. *Nat Chem*. 2014;6(1):75–80 (**Epub 2013/12/19. eng**).
34. Hänsel-Hertsch R, Beraldi D, Lensing SV, Marsico G, Zyner K, Parry A, et al. G-quadruplex structures mark human regulatory chromatin. *Nat Genet*. 2016;48(10):1267–72 (**Epub 2016/09/13. eng**).
35. Zhao Y, Zhang JY, Zhang ZY, Tong TJ, Hao YH, Tan Z. Real-time detection reveals responsive cotranscriptional formation of persistent intramolecular DNA and intermolecular DNA:RNA hybrid G-quadruplexes stabilized by R-loop. *Anal Chem*. 2017;89(11):6036–42 (**Epub 2017/04/28. eng**).
36. Stocks M. Intrabodies as drug discovery tools and therapeutics. *Curr Opin Chem Biol*. 2005;9(4):359–65 (**Epub 2005/06/28. eng**).
37. Zheng KW, Zhang JY, He YD, Gong JY, Wen CJ, Chen JN, et al. Detection of genomic G-quadruplexes in living cells using a small artificial protein. *Nucleic Acids Res*. 2020;48(20):11706–20 (**Epub 2020/10/13. eng**).
38. Simko EA, Liu H, Zhang T, Velasquez A, Teli S, Haeusler AR, et al. G-quadruplexes offer a conserved structural motif for NONO recruitment to NEAT1 architectural lncRNA. *Nucleic Acids Res*. 2020;48(13):7421–38.
39. Fukuhara M, Ma Y, Nagasawa K, Toyoshima F. A G-quadruplex structure at the 5' end of the H19 coding region regulates H19 transcription. *Sci Rep*. 2017;7(1):1–13.
40. Roach RJ, Garavís M, González C, Jameson GB, Filichev VV, Hale TK. Heterochromatin protein 1 $\alpha$  interacts with parallel RNA and DNA G-quadruplexes. *Nucleic Acids Res*. 2020;48(2):682–93.
41. Matsumura K, Kawasaki Y, Miyamoto M, Kamoshida Y, Nakamura J, Negishi L, et al. The novel G-quadruplex-containing long non-coding RNA GSEC antagonizes DHX36 and modulates colon cancer cell migration. *Oncogene*. 2017;36(9):1191–9.
42. Sahakyan AB, Murat P, Mayer C, Balasubramanian S. G-quadruplex structures within the 3' UTR of LINE-1 elements stimulate retrotransposition. *Nat Struct Mol Biol*. 2017;24(3):243–7.
43. Chang YC, Chiu C-C, Yuo C-Y, Chan W-L, Chang Y-S, Chang W-H, et al. An XIST-related small RNA regulates KRAS G-quadruplex formation beyond X-inactivation. *Oncotarget*. 2016;7(52):86713.
44. Booy EP, McRae EK, Howard R, Deo SR, Ariyo EO, Dzananovic E, et al. RNA helicase associated with AU-rich element (RHAU/DHX36) interacts with the 3'-tail of the long non-coding RNA BC200 (BCYRN1). *J Biol Chem*. 2016;291(10):5355–72.
45. Imperatore JA, Then ML, McDougal KB, Mihalescu MR. Characterization of a G-quadruplex structure in pre-miRNA-1229 and in its Alzheimer's disease-associated variant rs2291418: implications for miRNA-1229 maturation. *Int J Mol Sci*. 2020;21(3):767.
46. Podleśny-Drabiniok A, Marcora E, Goate AM. Microglial phagocytosis: a disease-associated process emerging from Alzheimer's disease genetics. *Trends Neurosci*. 2020;43(12):965–79.
47. Tan W, Yi L, Zhu Z, Zhang L, Zhou J, Yuan G. Hsa-miR-1587 G-quadruplex formation and dimerization induced by NH<sub>4</sub><sup>+</sup>(+), molecular crowding environment and jatrorrhizine derivatives. *Talanta*. 2018;1(179):337–43 (**Epub 2018/01/10. eng**).
48. Mirihana Arachchilage G, Kharel P, Reid J, Basu S. Targeting of G-quadruplex harboring pre-miRNA 92b by LNA rescues PTEN expression in NSCL cancer cells. *ACS Chem Biol*. 2018;13(4):909–14.
49. Tan W, Zhou J, Gu J, Xu M, Xu X, Yuan G. Probing the G-quadruplex from hsa-miR-3620-5p and inhibition of its interaction with the target sequence. *Talanta*. 2016;154:560–6.
50. O'Day E, Le MT, Imai S, Tan SM, Kirchner R, Arthanari H, et al. An RNA-binding protein, Lin28, recognizes and remodels G-quartets in the microRNAs (miRNAs) and mRNAs it regulates. *J Biol Chem*. 2015;290(29):17909–22.
51. Zhang J, Wang J, Li F, Zhu M, Wang S, Cui Q, et al. Normal expression of KCNJ11 is maintained by the G-quadruplex. *Int J Biol Macromol*. 2019;138:504–10 (**Epub 2019/07/22. eng**).
52. DeMarco B, Stefanovic S, Williams A, Moss KR, Anderson BR, Bassell GJ, et al. FMRP-G-quadruplex mRNA-miR-125a interactions: implications for miR-125a mediated translation regulation of PSD-95 mRNA. *PLoS ONE*. 2019;14(5):e0217275.
53. Maltby CJ, Schofield JP, Houghton SD, O'Kelly I, Vargas-Caballero M, Deinhardt K, et al. A 5' UTR GGN repeat controls localisation and translation of a potassium leak channel mRNA through G-quadruplex formation. *Nucleic Acids Res*. 2020;48(17):9822–39.
54. Bolduc F, Turcotte M-A, Perreault J-P. The small nuclear ribonucleoprotein polypeptide A (SNRPA) binds to the G-quadruplex of the BAG-1 5' UTR. *Biochimie*. 2020;176:122–7.

55. Ding X, Meng S, Zhou J, Yang J, Li H, Zhou W. Translational inhibition of  $\alpha$ -Neurexin 2. *Sci Rep*. 2020;10(1):1–12.
56. Agarwala P, Pandey S, Ekka MK, Chakraborty D, Maiti S. Combinatorial role of two G-quadruplexes in 5' UTR of transforming growth factor  $\beta$ 2 (TGF $\beta$ 2). *Biochim Biophys Acta Gen Subj*. 2019;1863(11):129416.
57. Al-Zeer MA, Dutkiewicz M, von Hacht A, Kreuzmann D, Röhrs V, Kurreck J. Alternatively spliced variants of the 5'-UTR of the ARPC2 mRNA regulate translation by an internal ribosome entry site (IRES) harboring a guanine-quadruplex motif. *RNA Biol*. 2019;16(11):1622–32.
58. Kawauchi K, Sugimoto W, Yasui T, Murata K, Itoh K, Takagi K, et al. An anionic phthalocyanine decreases NRAS expression by breaking down its RNA G-quadruplex. *Nat Commun*. 2018;9(1):1–12.
59. Herdy B, Mayer C, Varshney D, Marsico G, Murat P, Taylor C, et al. Analysis of NRAS RNA G-quadruplex binding proteins reveals DDX3X as a novel interactor of cellular G-quadruplex containing transcripts. *Nucleic Acids Res*. 2018;46(21):11592–604.
60. Guo S, Lu H. Conjunction of G-quadruplex and stem-loop in the 5' untranslated region of mouse hepatocyte nuclear factor 4- $\alpha$ 1 mediates strong inhibition of protein expression. *Mol Cell Biochem*. 2018;446(1):73–81.
61. Serikawa T, Eberle J, Kurreck J. Effects of genomic disruption of a guanine quadruplex in the 5' UTR of the Bcl-2 mRNA in melanoma cells. *FEBS Lett*. 2017;591(21):3649–59.
62. McAninch DS, Heinaman AM, Lang CN, Moss KR, Bassell GJ, Mihailescu MR, et al. Fragile X mental retardation protein recognizes a G quadruplex structure within the survival motor neuron domain containing 1 mRNA 5'-UTR. *Mol BioSyst*. 2017;13(8):1448–57.
63. Rouleau S, Glouzon J-PS, Brumwell A, Bisailon M, Perreault J-P. 3' UTR G-quadruplexes regulate miRNA binding. *RNA*. 2017;23(8):1172–9.
64. Ariyo EO, Booy EP, Dzananovic E, McRae EK, Meier M, McEleney K, et al. Impact of G-quadruplex loop conformation in the PITX1 mRNA on protein and small molecule interaction. *Biochem Biophys Res Commun*. 2017;487(2):274–80.
65. Newman M, Sfaxi R, Saha A, Monchaud D, Teulade-Fichou M-P, Vagner S. The G-quadruplex-specific RNA helicase DHX36 regulates p53 pre-mRNA 3'-end processing following UV-induced DNA damage. *J Mol Biol*. 2017;429(21):3121–31.
66. Koukouraki P, Doxakis E. Constitutive translation of human  $\alpha$ -synuclein is mediated by the 5'-untranslated region. *Open Biol*. 2016;6(4):160022.
67. Lee SC, Zhang J, Strom J, Yang D, Dinh TN, Kappeler K, et al. G-Quadruplex in the NRF2 mRNA 5' untranslated region regulates de novo NRF2 protein translation under oxidative stress. *Mol Cell Biol*. 2017;37(1):e00122-16.
68. Dai J, Liu Z-Q, Wang X-Q, Lin J, Yao P-F, Huang S-L, et al. Discovery of small molecules for up-regulating the translation of anti-amyloidogenic secretase, a disintegrin and metalloproteinase 10 (ADAM10), by binding to the G-quadruplex-forming sequence in the 5' untranslated region (UTR) of its mRNA. *J Med Chem*. 2015;58(9):3875–91.
69. Cammas A, Dubrac A, Morel B, Lamaa A, Touriol C, Teulade-Fichou M-P, et al. Stabilization of the G-quadruplex at the VEGF IRES represses cap-independent translation. *RNA Biol*. 2015;12(3):320–9.
70. Stefanovic S, DeMarco BA, Underwood A, Williams KR, Bassell GJ, Mihailescu MR. Fragile X mental retardation protein interactions with a G quadruplex structure in the 3'-untranslated region of NR2B mRNA. *Mol BioSyst*. 2015;11(12):3222–30.
71. Nie J, Jiang M, Zhang X, Tang H, Jin H, Huang X, et al. Post-transcriptional regulation of Nkx2-5 by RHAU in heart development. *Cell Rep*. 2015;13(4):723–32.
72. Crenshaw E, Leung BP, Kwok CK, Sharoni M, Olson K, Sebastian NP, et al. Amyloid precursor protein translation is regulated by a 3'UTR guanine quadruplex. *PLoS ONE*. 2015;10(11):e0143160.
73. Williams KR, McAninch DS, Stefanovic S, Xing L, Allen M, Li W, et al. hnRNP-Q1 represses nascent axon growth in cortical neurons by inhibiting Gap-43 mRNA translation. *Mol Biol Cell*. 2016;27(3):518–34.
74. Lago S, Nadai M, Ruggiero E, Tassinari M, Marušić M, Tosoni B, et al. The MDM2 inducible promoter folds into four-tetrad antiparallel G-quadruplexes targetable to fight malignant liposarcoma. *Nucleic Acids Res*. 2021;49(2):847–63.
75. Tan DJ, Winnerdy FR, Lim KW, Phan AT. Coexistence of two quadruplex-duplex hybrids in the PIM1 gene. *Nucleic Acids Res*. 2020;48(19):11162–71.
76. Hu M-H, Wu T-Y, Huang Q, Jin G. New substituted quinoxalines inhibit triple-negative breast cancer by specifically downregulating the c-MYC transcription. *Nucleic Acids Res*. 2019;47(20):10529–42.
77. Zhang X, Zhao B, Yan T, Hao A, Gao Y, Li D, et al. G-quadruplex structures at the promoter of HOXC10 regulate its expression. *Biochim Biophys Acta Gene Regul Mech*. 2018;1861(11):1018–28.
78. Huang H, Zhang J, Harvey SE, Hu X, Cheng C. RNA G-quadruplex secondary structure promotes alternative splicing via the RNA-binding protein hnRNP. *Genes Dev*. 2017;31(22):2296–309.
79. Tassinari M, Richter SN, Gandellini P. Biological relevance and therapeutic potential of G-quadruplex structures in the human noncoding transcriptome. *Nucleic Acids Res*. 2021;49(7):3617–33.
80. Mirihana Arachchilage G, Dassanayake AC, Basu S. A potassium ion-dependent RNA structural switch regulates human pre-miRNA 92b maturation. *Chem Biol*. 2015;22(2):262–72 (Epub 2015/02/03. eng).

## Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

