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REVIEW

Application of G-quadruplex targets in gastrointestinal cancers: Advancements, challenges and prospects

Zong-Qiang Han, Li-Na Wen

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Abstract

Genomic instability and inflammation are considered to be two enabling characteristics that support cancer development and progression. G-quadruplex structure is a key element that contributes to genomic instability and inflammation. G-quadruplexes were once regarded as simply an obstacle that can block the transcription of oncogenes. A ligand targeting G-quadruplexes was found to have anticancer activity, making G-quadruplexes potential anticancer targets. However, further investigation has revealed that G-quadruplexes are widely distributed throughout the human genome and have many functions, such as regulating DNA replication, DNA repair, transcription, translation, epigenetics, and inflammatory response. G-quadruplexes play double regulatory roles in transcription and translation. In this review, we focus on G-quadruplexes as novel targets for the treatment of gastrointestinal cancers. We summarize the application basis of G-quadruplexes in gastrointestinal cancers, including their distribution sites, structural characteristics, and physiological functions. We describe the current status of applications for the treatment of esophageal cancer, pancreatic cancer, hepatocellular carcinoma, gastric cancer, colorectal cancer, and gastrointestinal stromal tumors, as well as the associated challenges. Finally, we review the prospective clinical applications of G-quadruplex targets, providing references for targeted treatment strategies in gastrointestinal cancers.

Key Words: G-quadruplex; Pancreatic cancer; Liver cancer; Gastric cancer; Colorectal cancer; Gastrointestinal stromal tumor

Core Tip: G-quadruplexes are widely distributed in the human genome and have many functions. G-quadruplexes play double regulatory roles in transcription and translation. We focus on G-quadruplexes as novel therapeutic targets for gastrointestinal cancers. We summarize the application basis of G-quadruplexes in gastrointestinal cancers, including their distribution sites, structural characteristics, and physiological functions. We describe the current status of applications for the treatment of esophageal cancer, pancreatic cancer, hepatocellular carcinoma, gastric cancer, colorectal cancer, and gastrointestinal stromal tumors, as well as the associated challenges. We review prospective clinical applications of G-quadruplex targets, providing references for targeted treatment in gastrointestinal cancers.

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INTRODUCTION

Gastrointestinal cancers seriously affect the quality of life of patients and are among the cancers with the highest incidence and mortality worldwide. There currently remains a lack of effective therapeutic methods for these cancers, despite the development of many anticancer strategies. This is mainly because the etiology and molecular mechanisms associated with the occurrence and development of many cancer types are unclear, despite tumor immunotherapy and molecular targeted therapies having achieved promising results. In the multistep development of various human cancers, 14 characteristics were summarized as the latest hallmarks of cancer: Sustaining proliferative signaling, evading growth suppression signals, avoiding immune destruction, enabling replicative immortality, tumor-promoting inflammation, activating invasion and metastasis, inducing or accessing the vasculature, genomic instability and mutation, resisting cell death, deregulating cellular metabolism, unlocking phenotypic plasticity, nonmutational epigenetic reprogramming, polymorphic microbiomes, and senescent cells[1]. Genomic instability and inflammation have been considered as the two enabling characteristics that allow cancer to acquire these hallmarks[2]. Importantly, inflammation itself can induce genomic instability[3]. The role of inflammation in the transformation of gastrointestinal cancers, such as gastric, intestinal and liver cancers, should not be ignored. Hence, in the future, anticancer strategies targeting genomic instability may have potentially broad applications for the treatment of cancer. The molecular and cellular elements affecting genomic instability may become effective anticancer targets.

In 1962, the unusual four-stranded helix structures of guanine-rich DNA sequences with a high tendency to self-assemble into planar guanine quartets (G-quartets) were first reported and named as G-quadruplexes[4]. Afterwards, DNA G-quadruplexes were found in telomeres[5], oncogene promoters[6,7], microsatellite fragments[8], and additional regions. In 1992, tetraplex formation of nucleotide sequences in the 3′ terminus of the 5s RNA were found in *Escherichia coli* in the presence of K^+ solution[9]. Subsequently, > 3000 RNA G-quadruplex component elements in the mRNA 3′ and 5′ untranslated regions (UTRs)[10,11] and exons[12,13], as well as in other noncoding RNAs[14], were discovered in the human genome. As a nucleic acid secondary structure, a G-quadruplex differs from the typical A-, B-, C- or Z- of duplex DNA, conventional RNA, and was the supplement to nucleic acid structure type. The crystal or solution structures of various DNA or RNA G-quadruplexes have been increasingly resolved, with their physiological functions gradually clarified, especially their roles in various forms of cancers, such as breast cancer, osteosarcoma, and cervical carcinoma[3,15-19]. G-quadruplexes can regulate DNA replication[20,21], repair[22], methylation[23], and gene transcription and translation[24], and correlate with genomic instability[3,25]. In this review, we summarize the literature on G-quadruplexes and their ligands from 1962 to 2023 and describe G-quadruplex characteristics, including the existing sites, structural details, and physiological functions, and their potential applications in gastrointestinal cancer therapy. In addition, we summarize the challenges and prospects of targeting G-quadruplexes in digestive tumors to potentially prevent and treat gastrointestinal cancers.

BASIS OF THERAPEUTIC APPLICATIONS OF G-QUADRUPLEXES IN GASTROINTESTINAL CANCERS

The clinical application value of biological molecules is dependent upon their biological functions, which are affected by intracellular distribution, molecular structure and other properties. Therefore, such molecular characteristics form the basis for clinical application potential, as shown in Figure 1.

Potential G-quadruplex sites in humans

Potential G-quadruplex structures in the human genome can be predicted *via* computer analysis by retrieving the pattern sequences ($G_{\geq 3}N_{1\text{-}7}G_{\geq 3}N_{1\text{-}7}G_{\geq 3}N_{1\text{-}7}G_{\geq 3}$)[26]. They can also be formed with less than three guanines contrary to this dogma [27]. With the development of G-quadruplex-specific antibodies, fluorescent probes, sequencing technology, and genomic mapping, G-quadruplex structures are being increasingly detected and visualized in cells[28-33]. Currently, at least 700000 potential G-quadruplex structures have been inferred to exist in humans[34-36]. Telomeric DNA was the first

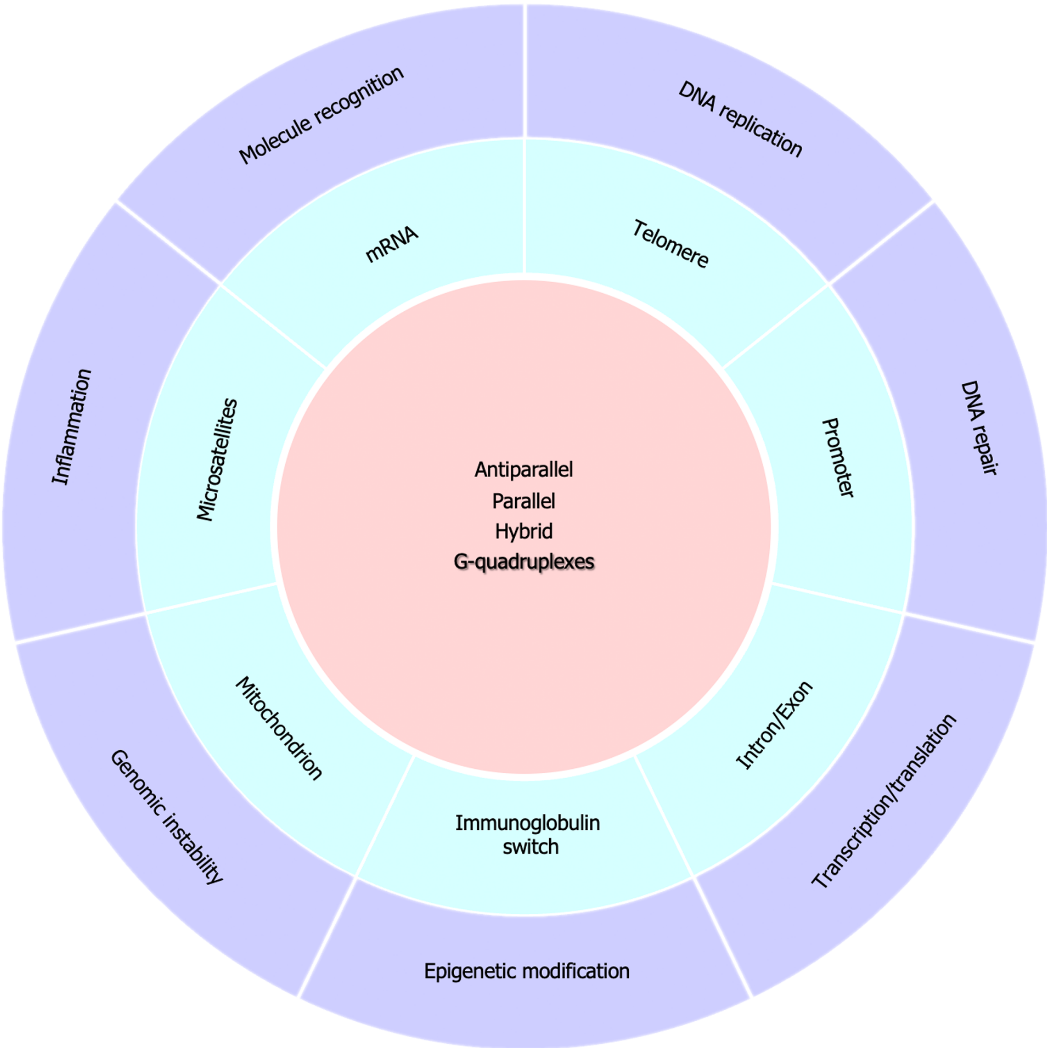

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Figure 1 Application basis of G-quadruplex targets in gastrointestinal cancers: G-quadruplex characteristics. From the inner ring to the outer ring, there are basic structure types, distribution sites and physiological functions of G-quadruplexes.

biologically-related G-quadruplex target investigated in detail[37] and was considered to have the highest abundance of potential G-quadruplex structures. The 5000-10000 bp of tandemly repeated sequence (TTAGGG) contained in telomeres can fold into a G-quadruplex to regulate telomere maintenance[38,39]. Maintaining its structural stability can help inhibit the activity of telomerase and thus prevent the unlimited proliferation of tumor cells[40]. In addition to telomeres, genome-wide sequencing analyses have suggested that more than 8000 potential G-quadruplexes are likely enriched in promoter regions spanning 1 kb upstream of the transcription initiation sites in humans[41,42]. In the past, close attention was paid to proto-oncogene promoter G-quadruplexes, including Kirsten rat sarcoma viral oncogene homologue (*KRAS*) [43], *HRAS*[44], *c-MYC*[45], *c-KIT*[46], *RET*[47], *MST1R*[48], and others. G-quadruplexes in promoter regions of carcinoma-related genes were studied as well, such as B-cell lymphoma 2 (*BCL2*)[49], hypoxia inducible factor 1 subunit alpha (*HIF1a*)[50], vascular endothelial-derived growth factor (*VEGF*)[51], platelet-derived growth factor subunit A (*PDGFA*)[52], PDGF receptor-β (*PDGFR-β*)[53], human telomerase reverse transcriptase (*hTERT*)[54], nuclear factor (erythroid-derived 2)-like 2[55], *SMARCA4*[56], and multidrug resistance protein 1[57]. Recent studies have indicated that G-quadruplexes also exist in promoter regions of *MYH7β* gene and are associated with various myopathies[58], as well as in *CSTB* gene, and are related to progressive myoclonus epilepsy type 1[59]. Moreover, there were G-quadruplex-forming sequences (GGGGCC) in intron 1 of the *C9orf72* gene, which was the usual hereditary factor of amyotrophic lateral sclerosis and frontotemporal dementia[60]. Similar sequences were also found in other genes, for example, (GGCCT) in the first intron of *NOP56* relevant to spinocerebellar ataxia (SCA36)[61], (CCCCATGGTGGTGGCTGGGGACAG) in the coding exon of the *PRNP* gene indicating Creutzfeldt–Jakob disease[62], TAGGGCGGGAGGGAGGGAA in the first intron of the *N-myc* gene[63], and $(GGGT)_4$ in human microsatellites[8]. Additionally, abundant potential G-quadruplex formation sites exist in mRNAs (especially in the 5′ UTRs) or microRNAs. For instance, mRNA G-quadruplexes reportedly include *VEGF*[64], *FMR1*[65], *MMP16*[66], transforming growth factor-β (*TGFβ2*)[10], neuroblastoma RAS viral oncogene homolog (*NRAS*)[67], insulin-like growth factor 2[68], telomere repeat binding factor 2 (*TRF2*)[69], *PIM1*[70], beta-site amyloid precursor protein cleaving enzyme 1[71] and *YY1*[72]. G-quadruplex structures have recently been explored in miR-92a[73], miR-1229[74] and miR-1587[75]. G-quadruplexes have also been discovered in immunoglobulin switches, microsatellites, and mitochondria genes. However, when and where the potential G-quadruplex structures can actually form and exert corresponding physiological functions *in vivo* depend on environmental conditions, which require further investigation.

Structural characteristics of G-quadruplexes

Different from the Watson-Crick base pairing regulation of double-stranded DNA, three to four guanines assemble into a G-quartet by Hoogsteen hydrogen-bonding in a square planar platform. The G-quartets then further stack on top of one another to form G-quadruplexes, which remain stable by monovalent cations in the central ion channel[76]. Because of the different number and spatial arrangement of bases, G-quadruplex structures have obvious polymorphisms. X-ray diffraction and high-field nuclear magnetic resonance spectroscopy are two effective methods for understanding the crystal and solution structures, which can be categorized as intramolecular or intermolecular G-quadruplexes. An intramolecular G-quadruplex is unimolecular and previous studies have confirmed that there are three basic types according to the orientation of the G-quartet: Parallel structure, antiparallel structure, and hybrid structure[77]. These different structures have varying levels of stability, which may affect their respective functions. Because of the restrictions of the external environment and central cation, a G-quadruplex sequence may present multiple configurations. For the human telomeric sequence, crystal or solution structural elucidation revealed that in the presence of K^+ solution, the G-quadruplex had parallel, antiparallel, hybrid-2, and hybrid-1 configurations, with an intermediate of two-tetrad[18,78-81]. However, in the presence of Na^+ solution, one unfolded state and three G-quadruplex-related configurations are observed, and the structure can interconvert between these forms[82]. *KRAS*, *c-MYC*, *VEGF*, *PDGFR-β* and *HIF1a* promoter G-quadruplexes take on parallel structures in K^+ solution[50,76], *BCL2* promoter G-quadruplexes adopt the hybrid-2 or parallel conformation in K^+ solution[76], and *c-KIT* promoter sequences can form a parallel or antiparallel G-quadruplex[83,84]. G-quadruplex structures present in other sites, such as in mRNAs, also conform to these three basic structural types. For intramolecular G-quadruplexes, more than two unimolecular G-quadruplex sequences can assemble into intermolecular parallel G-quadruplexes[18,58,75].

Physiological functions of G-quadruplexes

G-quadruplexes and DNA replication: Current research supports two seemingly opposing views on how G-quadruplexes can influence DNA replication: One view suggests that the G-quadruplex motif is necessary for replication initiation, while the other argues that a G-quadruplex is an obstacle to replication. Evidence supporting the former view is that 70%-90% of replication origins are preceded by a potential G-quadruplex-forming sequence, called the origin G-rich repeated element, which is 250-300 bp upstream of the replication initiation site in the non-nucleosome region[72,85]. Either deleting these elements in several model origins or introducing point mutations that affect G-quadruplex stability may reduce replication initiation activity in cells[86]. In addition, G-quadruplexes can recruit replication activators to play a role in DNA replication[87]. The latter view also has strong evidence, including that small molecular ligands targeting G-quadruplexes can result in DNA damage[88]. Additionally, it was demonstrated that the helicase, chromatin-remodeling protein ATRX, and human CTC1-STN1-TEN1 complex prevented replication defects by unwinding G-quadruplexes[89-92]. There were two possible conclusions regarding this argument. First, a G-quadruplex structure preferentially formed in the firing origin rather than the licensing origin[93,94]. Second, the negative regulation of DNA replication mediated by G-quadruplexes mostly occurred under pathological conditions, such as in the presence of G-quadruplex ligands or absence of ATRX. The negative effects of G-quadruplexes on DNA may be counteracted by unwinding proteins, such as helicase, in wild type cells under undisturbed situation[21].

G-quadruplexes and DNA repair: DNA damage can be triggered by exogenous stimuli, such as physical and chemical factors, or endogenous stress, which includes reactive oxygen species (ROS) production, replicative stress, and the formation of nucleic acid secondary structure. In addition to telomeres, promoters and transcriptional start sites, G-quadruplexes are enriched in DNA double-strand break (DSB) sites during mitosis and meiosis, and G-quadruplex formation may induce DNA damage and negatively impact effective DNA repair mechanisms[22,95]. However, G-quadruplexes can sometimes promote certain repair pathways under specific conditions. There are six main pathways involved with DSB repair over DNA replication: Homologous recombination (HR), nonhomologous end joining, base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), and translesion synthesis (TLS). One model suggested that stabilization of G-quadruplexes can active HR, leading to bypass/repair of G-quadruplex-mediated DNA damage[22]. As a sensor for endogenous oxidative damage of DNA, G-quadruplexes may provide feedback to drive BER to promote genomic stability under oxidative stress[96]. Zoo1 could assist NER function and regulate the selection of DNA repair pathways near G-quadruplex structures[97]. MMR activation was not restricted when G/T and G-quadruplex mismatch were in close proximity[98], and the stable G-quadruplex structure could inhibit the activity of endonuclease of MutL and indirectly interfere with the MMR process[99].

G-quadruplexes and transcription and translation: Potential G-quadruplex forming-sequences are frequently enriched in DNA promoter regions and the 3′ or 5′ UTRs, providing an opportunity for regulation of transcription or translation. For highly expressed cancer-related genes, proteins such as nucleolin and small molecular ligands that promote G-quadruplex formation can induce transcriptional repression. However, proteins that unwind G-quadruplexes such as the nucleoside diphosphate kinase NM23H2, poly ADP-ribose polymerase and RecQ family helicase can lead to transcriptional activation of target genes[100,101]. Moreover, putative G-quadruplex-forming sequences were also found at the docking sites of transcription factors SP1 and c-MYC associated zinc-finger protein (MAZ), which may help recruit SP1 and MAZ and facilitate transcription in cancer progression[102,103]. In noncancerous cells, studies have shown that G-quadruplexes can directly interfere with mitochondrial genome replication, transcription, and respiratory function[104]. Therefore, a G-quadruplex is a key factor that can regulate gene transcription. Similarly, RNA G-quadruplexes can control translation. For instance, oxymatrine inhibited the translation of *VEGFA* mRNA in human cervical cancer cells by selectively binding to the G-quadruplex structure in *VEGFA* 5′ UTRs[105]. Additionally, DEAH box polypeptide 36 (DHX36) can bind to 5′ UTRs G-quadruplexes and control translation to promote muscle stem cell regeneration[106]. Thus, G-quadruplexes play significant roles in gene transcription and translation.

G-quadruplexes and epigenetic modifications: C-5 methylation of cytosine by DNA methyltransferase DNMT1, DNMT3A and DNMT3B is a key DNA epigenetic modification in mammalian development and disease. About 90% of CpGs can be highly methylated, but CpG islands (CGIs), found in dense guanine-cytosine-rich regions, largely lack methylation and are universally present in the promoter regions of genes[107]. CGIs can be progressively methylated during certain biological events, such as aging[108] and cancer[109], but the underlying regulatory mechanisms are not fully clear. Studies have shown that G-quadruplex structures are present in CGIs and are closely related to reduce levels of CGIs methylation in the human genome[110]. G4-chromatin immunoprecipitation sequencing (G4-ChIP-seq) analysis indicated that G-quadruplex structures were colocalized with DNMT1 and inhibited methylation by inhibiting activity of this enzyme[110]. Recent studies have shown that the methylation efficiency decreased with increasing G-quadruplex stability, and the degree of methylation can be controlled by adjusting the G-quadruplex topology[111].

In addition to DNA methylation, histone modification is also an important epigenetic regulation. The local conformations and biological functions of G-quadruplexes can be regulated by their specific binding proteins. For example, RNA G-quadruplexes and RNA-binding proteins participate in telomere maintenance and transcriptional regulation through histone modifications. G-quadruplex RNA-binding proteins, such as translocated in liposarcoma/fused in sarcoma and TRF2, can promote the trimethylation of histone H3 at lysine 9 in telomere histones through G-quadruplex telomeric repeat-containing RNA (TERRA)[112,113]. G-quadruplex TERRA possibly regulates methylation and demethylation of histones in telomeric DNA, and can act as a noncompetitive inhibitor to suppress lysine specific histone demethylase-mediated histone demethylation[114]. Polycomb repressive complex 2 (PRC2) interactions with TERRA can catalyze the trimethylation of histone H3 at lysine 27 (H3K27me3), and G-quadruplex RNA can specifically prevent PRC2 from interacting with genes in human and mouse cells to block methylation at H3K27[115]. These mechanisms work together to maintain telomere length and chromatin function.

G-quadruplexes and genomic instability: DNA is vulnerable to damage from various types of endogenous and exogenous stimuli. This can hinder DNA replication and induce genomic instability, which includes point mutations, insertions, deletions, inversions, translocations, expansions/contractions of repeated sequences, gross chromosomal rearrangements, aneuploidy and other characteristics. Such genomic instability is often observed in cancer and can be induced by G-quadruplexes. G-quadruplexes are enriched at regions of base substitutions, insertion-deletion mutations, and chromosome translocation breakpoints that are associated with a variety of human cancers, such as colon cancer, and is the main inducing factor of carcinogenic transformation[116-118]. The instability of potential G-quadruplex-forming sequences increases in a transcription-dependent manner, as transcription can provoke genomic instability of G-quadruplexes by releasing single-stranded DNA, which is easy to fold into secondary structures[117,119].

G-quadruplex and inflammation: G-quadruplexes are correlated with inflammation. Studies have shown that there was a high frequency of potential G-quadruplex formation sequences in the promoter regions of many inflammatory factors, such as tumor necrosis factor, TGF-β, interleukin (IL)-6, IL-12, IL-17, the XC and TAFA family chemokines, and β-chain family cytokines[120]. G-quadruplexes are also distributed in the binding sites of transcription factors involved in inflammatory and immune processes, including nuclear factor nuclear factor kappa B1, interferon regulatory factor 5, transcription factor p65, transcription factor RelB, and nuclear factor of activated T cells 5[120]. In addition, genes containing G-quadruplex structures that can regulate and participate in inflammatory-related processes have been identified through experimental studies[121]. G-quadruplexes can trigger inflammatory reactions by upregulating proinflammatory cytokines, making these structures a marker of increased inflammation and a contributor to inflammatory diseases development[121]. However, another study suggested that G-quadruplexes can interfere with switch-like recombination in B cells to alleviate allergic inflammation[122]. Collectively, this evidence suggests that G-quadruplexes may be a potential target for treating inflammation-related diseases.

Ion and molecule recognition functions of G-quadruplexes: The stability of G-quadruplex structure needs to be maintained by the monovalent cations located in the central ion channel, allowing the G-quadruplex sequence to specifically recognize monovalent cations such as K^+ and Na^+. In addition, because the specific G-quadruplex-forming sequence can fold into a special conformation and the fluorescence emission of some small molecules is significantly enhanced after binding with G-quadruplexes, G-quadruplexes could be used to identify small molecular ligands (berberine, porphyrin, and more) or proteins (thrombin, nucleolin, and more) that can specifically bind to them[16,57,123,124] or assist imaging. Therefore, G-quadruplexes have been widely used as recognition elements to construct biosensors for detecting targeting ions and molecules, such as tumor biomarkers, in tumor diagnosis, as well as targeting agents or drug carriers of anticancer drug delivery systems for tumor treatment[125,126]. In such applications, the G-quadruplex sequences are also called aptamers.

APPLICATION OF G-QUADRUPLEX TARGETS IN GASTROINTESTINAL CANCER THERAPIES

The above complex biological functions of G-quadruplexes imply that they have broad application prospects for the diagnosis and treatment of gastrointestinal cancers. The role of a G-quadruplex as a recognition element in the molecular diagnosis of gastrointestinal cancers will not be discussed in this review. The application of G-quadruplexes in therapy is mainly discussed from two perspectives: (1) The therapeutic effect of small molecule ligands and biomolecules targeting G-quadruplexes to regulate gene transcription; and (2) The therapeutic effect of G-quadruplex sequences for molecular recognition functions.

Application of small molecule ligands or biomolecules targeting G-quadruplexes in the treatment of gastrointestinal cancers

Esophageal cancer: Esophageal cancer (EC) is a gastrointestinal disease with high mortality rates. Surgery is the first choice of treatment for resectable EC cases, but neoadjuvant chemotherapy can improve the 5-year survival rate without increasing postoperative complications. Targeting G-quadruplexes may provide a new perspective for treating EC, although relevant research on this is currently limited. The telomere is an early G-quadruplex target. The G-quadruplex ligand 2,6-bis[3-(N-piperidino) propionamido] anthracene-9,10-dione, which is also considered to be a telomerase inhibitor, can shorten telomeres and exert antiproliferative and proapoptotic effects in both BIC-1 and SEG-1 EC cell lines [127]. A recent study found that zinc benzoate terpyridine complexes (1-6) in combination with G-quadruplex sequence (G2T4G2CAG2GT4G2T) resulted in various degrees of antiproliferative effects in the EC cell line Eca-109[128] (Table 1). Hence, further exploration of a G-quadruplex-related treatment strategy in EC is needed.

Pancreatic cancer: Pancreatic cancer (PC) is a refractory tumor disease with poor prognosis among cancers. About 97% of PC cases are accompanied by alterations of genes and 90% have *KRAS* oncogene mutations, which are essential for initiation of pancreatic ductal adenocarcinoma. Because *KRAS* can drive oncogene addiction, inhibiting gene mutation and downregulating gene expression are reasonable ways to block PC progression. Many attempts have been paid to target *KRAS* oncogenes, but clinically useful therapies are still limited. The mutant KRAS protein has attracted much attention, causing other approaches involving targeting *KRAS* transcription to not be fully explored. Additionally, telomere, heat shock protein 90 (*HSP90*), *c-MYC*, *Bcl-2* and others are important genes that affect cancer cell fate. Therefore, inhibiting the transcription of PC-related genes may be effective. There are G-quadruplex configurations in telomere and the promoter regions of *HSP90*, *KRAS*, *c-MYC* and *Bcl-2*, that are potential targets. Stable G-quadruplex structure usually acts as an obstacle to gene transcription. Small molecular ligands that stabilize G-quadruplex conformation can exhibit clear anticancer effects in PC.

Naphthalene diimide compounds are part of an important ligand set. A series of tetrasubstituted naphthalene diimide ligands tended to make telomeric G-quadruplexes fold into a parallel conformation, preventing binding of human protection of telomeres 1 and topoisomerase IIIα with telomeric DNA, triggering cytotoxicity in multiple PC cell lines [129]. Tetrasubstituted naphthalene diimide derivatives (compounds 3d) retain high affinity to human telomeric G-quadruplexes, upregulate DNA damage responsive genes such as *CDKN1A* and *DDIT3*, downregulate telomere maintenance genes such as *POT1* and *PARP1*, and induce cellular senescence[130]. Tetrasubstituted naphthalene diimide isomer ligands (compounds 2-5) are more inclined to stabilize telomeric G-quadruplex structure and improve antiproliferative potency[131]. Tetrasubstituted naphthalene diimide derivative (MM41) combines with and stabilizes G-quadruplex structure and downregulates expression levels of *BCL-2* and *KRAS* to promote apoptosis and decrease tumor growth of MIA-Pa-Ca2 xenografts[132,133]. Tetrasubstituted naphthalene diimide derivative (CM03) causes DNA damage and promotes the presence of nuclear G-quadruplexes in PANC-1 cells; inhibits expression of *GLI4*, *PLXNA1*, *PRKCZ* and *MAPK11*; partitions *PARD6A*, and *CBFA2T3* in MIA PaCa-2 and PANC-1 cells; and decreases tumor growth of MIA-Pa-Ca2 xenografts[133-135]. Tetrasubstituted naphthalene diimide derivative (SOP1812) was verified to have antiproliferative activity by combining with *hTERT* and telomere G-quadruplexes[135]. Another naphthalene diimide derivative (BMSG-SH3) decreases telomerase activity, inhibits *HSP90* expression, and reduces tumor growth of MIA-Pa-Ca2 xenografts by 50% through maintaining the stability of telomere and *HSP90* promoter G-quadruplex structures[136].

Porphyrin compounds are part of another important ligand set. A cationic alkyl-substituted porphyrin compound C14 binds to the *KRAS* promoter G-quadruplex, protoxidizes the guanines, suppresses gene expression and eventually leads to growth inhibition of PC cell line PANC-1 under photosensitive conditions[137]. Alkyl cationic porphyrins can promote apoptosis *in vitro* and restrict metabolism and tumor growth *in vivo* by targeting G-quadruplexes of *KRAS* and *NRAS* mRNAs[138]. Porphyrin derivative octaacetyl and tetrakis can both induce apoptosis and block metastasis by inhibiting epithelial to mesenchymal transition through stabilizing *KRAS* promoter G-quadruplexes and downregulating *KRAS* expression levels[139], while porphyrin derivative (5Me) may regulate cell proliferation and cell cycle progression by interacting with telomere, *Bcl-2*, *c-MYC* and *KRAS* G-quadruplexes[140]. Previous studies have shown that TMPyP4 can bind to intermolecular G-quadruplexes to arrest cell proliferation and induce both cellular senescence and apoptosis in MIA PaCa-2 cells[140].

Different from TMPyP4, telomestatin can bind to intramolecular G-quadruplexes and control cell proliferation, senescence and apoptosis in MIA PaCa-2 cells[141]. The benzophenanthridine alkaloid nitidine combines with the *KRAS* promoter G-quadruplex and stabilizes its structure, further downregulating *KRAS* expression levels and inducing cytotoxicity in AsPC-1, BxPC-3, MIA PaCa-2, and PANC-1 cells[142]. 4,11-bis(2-Aminoethy-llamino)anthra[2,3-b]furan-5,10-dione(2a),11-bis(2-aminoethylamino)anthra[2,3b]thiophene-5,10-dione (2b) stabilizes *KRAS* RNA G-quadruplexes, inhibits its translation, and induces apoptosis and growth inhibition of PANC-1 cells[143]. Unsymmetrical bisacridines derivatives can inhibit the proliferation of cancer cells *in vitro* and *in vivo* by increasing the stability of telomere, *c-MYC* and *KRAS* G-quadruplexes[144]. Copper(ii) l/d-valine-(1,10-phen) complexes (complex 1a, 1b) induce cytotoxicity of

Table 1 Overviews of investigations on the effects of small molecule ligands or biomolecules based on G-quadruplex targets in esophageal cancer

Ligands/biomolecules	Cell lines	Targeting gene/G-quadruplex	Effects on G-quadruplex	Effects on genes	Anticancer phenotypes	Ref.
2,6-bis[3-(N-Piperidino) propionamido] anthrace- ne-9,10-dione	BIC-1, SEG-1	Telomere	Not detected	Shortened telomeres	Inhibited telomerase activity, arrested cell proliferation, reduced colony number and size, and promoted cell apoptosis	[127]
Zinc benzoate erpyridine complexes (1-6)	Eca-109	G2T4G2CA, G2GT4G2T	Bound with G-quadruplex	Not detected	Inhibited cell proliferation	[128]

BxPC3 and AsPC1 cells from its affinity with telomeric G-quadruplexes[145]. CX-5461, the ligand of telomere, *c-MYC* and *c-kit* G-quadruplexes, also exhibits antiproliferative activity, and phase I/II clinical trials of CX-5461 as an anticancer drug have been launched[146,147]. A small molecular fluoroquinolone derivative CX-3543 (quarfloxin) can decrease tumor growth of MIA PaCa-2 xenografts by disrupting nucleolin/G-quadruplex complexes on rDNA and inhibiting rRNA synthesis[148,149]. FDA-approved antihelminthic pyrvinium pamoate inhibits mitochondrial RNA transcription and tumor growth by selectively binding to mitochondrial G-quadruplexes[150]. NSC 317605 and novel indoloquinolines derived from it show *KRAS* G-quadruplex-dependent cytotoxicity in PC cell lines[151]. Two sets of quinazoline-pyrimidine derivative ligands have been shown to prevent tumor growth *via* targeting telomere, *c-MYC*, *c-kit*, *KRAS* and *BCL-2* G-quadruplexes[152].

Some small molecules can play anticancer roles in PC mainly by stabilizing G-quadruplex structures to inhibit gene transcription. However, in addition, some proteins can promote PC progression by destabilizing G-quadruplexes to support gene transcription. For example, integrin linked kinase (ILK) can stimulate *KRAS* expression *via* destabilization of G-quadruplexes mediated by *hnRNPA1* in the promoter. This in turn affected ILK expression levels, with transcriptional activation mediated by E2F1. This has been called the KRAS-E2F1-ILK-hnRNPA1 regulatory loop, which can result in aggressive phenotypes in the tumor microenvironment[153-155]. Under oxidative stress conditions, poly (ADP-ribose) polymerase 1 (PARP-1) is recruited and binds to *KRAS* promoter G-quadruplexes, which favors the recruitment of MAZ and hnRNPA1 to the *KRAS* promoter by activating a ROS-G-quadruplex-PARP-1 axis. This ultimately results in stimulation of *KRAS* transcription[156]. Different from this mechanism, the G-quadruplex-binding protein apurinic/apyrimidinic endonuclease 1 can also bind to *KRAS* G-quadruplexes. However, it maintains the structural stability and recruits MAZ to promote *KRAS* upregulation *in vivo* and *in vitro*[157]. Moreover, polypurine reverse Hoogsteen hairpins (PPRHs) can suppress gene transcription and cell proliferation by promoting the formation of *KRAS* and *c-MYC* G-quadruplexes in PC cells[158,159].

In summary, the G-quadruplex targets of PC include *KRAS*, *KRAS* mRNA, telomere, *HSP90*, *hTERT*, *Bcl-2*, *c-MYC*, and mitochondrial G-quadruplexes, the regulatory functions of which involve transcription and translation. Proteins that can promote oncogene transcription through G-quadruplexes are also expected to become potential anticancer targets. All details are described in Table 2.

Hepatocellular carcinoma: Different from the genetic pathogenesis of PC, specific mutations in proto-oncogenes that can induce hepatocellular carcinoma (HCC) have not been identified. However, anticancer strategies for HCC involving oncogene G-quadruplexes are still being explored. At present, G-quadruplex ligands targeting *c-MYC*, *c-kit* and *HERC5* have been synthesized and verified for potential application in HCC treatment. Platinum (II) complexes with tridentate ligands, prolinamide derivatives containing triazole, a series of novel 9-O-substituted-13-octylberberine derivatives and novel 9-N-substituted-13-alkylberberine derivatives were all tested and found to have good antiproliferative activities in HepG2 cells, mainly from their good affinity with *c-MYC* promoter G-quadruplexes and their improved structural stability[160-163]. A series of thiazole orange derivatives were synthesized to effectively bind to telomeric G-quadruplexes, which can stabilize the structures and exhibit cytotoxicity in HCC cell lines[164]. The peptidomimetic ligands showed high affinity to *c-kit1* G-quadruplexes also exhibit antiproliferative and proapoptotic properties in HepG2 cells[165]. A 7,11-disubstituted quinazoline derivative HZ-6d targeting *HERC5* G-quadruplexes showed anticancer effects *in vivo* and *in vitro* through downregulation of *HERC5* expression[166].

Viral hepatitis is a primary cause of HCC. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections can develop into chronic hepatitis and then cirrhosis, eventually leading to HCC. Therefore, early intervention is an effective strategy for delaying HCC progression. In recent years, G-quadruplexes have become a potential target for antiviral therapy. RNA helicase dead box polypeptide 5 can facilitate mRNA translation of *STAT1* by unwinding the RNA G-quadruplex structure at the 5′ end of the 5′ UTR, subsequently stimulating the antiviral effects of interferon-α in HBV-infected hepatoma cells[167]. Additionally, cellular nucleolin can directly interact with viral core RNA G-quadruplexes, thereby suppressing the replication and expression of wild-type HCV[168]. All details are described in Table 3.

Gastric cancer: Gastric cancer (GC) ranked third worldwide in malignant tumor mortality rates in 2020. Most patients had late stage disease at diagnosis. For advanced GC, chemotherapy is the preferred option, but the associated adverse effects should not be ignored. It is necessary to seek new methods to treat GC, which could include targeted drug therapies based on G-quadruplexes. Small molecules selectively binding to *c-kit*, telomere and *BCL-2* G-quadruplexes have been found to antagonize GC. For example, benzo[a]phenoxazines and quinazolone derivatives display cytotoxicity

Table 2 Overviews of investigations on the effects of small molecule ligands or biomolecules based on G-quadruplex targets in pancreatic cancer

Ligands/biomolecules	Cell lines	Targeting gene/G-quadruplex	Effects on G-quadruplex	Effects on genes	Anticancer phenotypes	Ref.
Tetrasubstituted naphthalene diimide ligands	PANC-1, MIA PaCa-2, HPAC, BxPc-3	Telomere	Induced formation of a parallel G-quadruplex	Inhibited the binding of hPOT1 and topoisomerase IIIα to telomeric DNA	Cytotoxicity	[129]
Tetrasubstituted naphthalene diimide derivatives (compounds 3d)	MIA PaCa-2	Telomere	Retained high affinity to human telomeric G-quadruplex	Upregulated some DNA damage responsive genes, downregulated some telomere maintenance genes	Induced cellular senescence but did not inhibit telomerase activity	[130]
Naphthalene diimide isomer ligands (compounds 2-5)	MIA PaCa-2, PANC-1	*HSP90*	Stabilized G-quadruplex structure	Not detected	Inhibited cell proliferation	[131]
Tetrasubstituted naphthalene diimide derivative (MM41)	MIA PaCa-2	*BCL-2, K-RAS*	Bound and stabilized G-quadruplex structure	Downregulated expression of *BCL-2, K-RAS*	Promoted cell apoptosis, decreased tumor growth of MIA-Pa-Ca2 xenografts	[132]
Tetrasubstituted naphthalene diimide derivative (CM03)	MIA PaCa-2, PANC-1	Not detected	Increased presence of nuclear G-quadruplex	Induces DNA damage, downregulated expression of *Gli4, PLXNA1, PRKCZ, MAPK11, PARD6A, CBFA2T3*	Decreased tumor growth of MIA-Pa-Ca2 xenografts	[133-135]
Tetrasubstituted naphthalene diimide derivative (SOP1812)	MIA PaCa-2, PANC-1, Capan-1, BXPC-3	*hTERT*, telomere	Had affinity with G-quadruplex	Downregulated expression of *WNT5B, DVL1, AXIN1, APC2, GLI1, MAPK11, BCL-2, hTERT*	Inhibited cell proliferation, reduced MIA PaCa-2 xenograft growth	[135]
Tetrasubstituted naphthalene diimide derivative (BMSG-SH3)	MIA PaCa-2	*HSP90*	Stabilized G-quadruplex structure	Not detected	Reduced telomerase activity and HSP90 expression, 50% decreased tumor growth of MIA-Pa-Ca2 xenografts	[136]
Cationic alkyl-substituted porphyrin compound C14	PANC-1	*KRAS*	Bound with G-quadruplex and protoxidized the guanines	Downregulated expression of *KRAS*	Induced cell growth arrest	[137]
Alkyl cationic porphyrins	MIA PaCa-2, PANC-1	*KRAS* mRNA, *NRAS* mRNA	Bound G-quadruplex	Downregulated expression of *KRAS, NRAS* only if photoactivated	Activated apoptosis, reduced the metabolic activity of pancreatic cancer cells and the growth of a PANC-1 xenograft	[138]
Porphyrin derivative (Octaacetyl)	PANC-1, MIA PaCa-2	*KRAS*	Bound and stabilized G-quadruplex	Downregulated expression of *KRAS*	Cytotoxicity, induced apoptosis, blocked metastasis by inhibiting epithelial to mesenchymal transition	[139]
Porphyrin derivative (Tetrakis)	PANC-1, MIA PaCa-2	*KRAS*	Bound and stabilized G-quadruplex	Downregulated expression of *KRAS*	Cytotoxicity, induced apoptosis, blocked metastasis by inhibiting epithelial to messenchymal transition	[139]
Porphyrin derivative (5Me)	PANC-1	Telomere, *Bcl-2*, *c-MYC*, *KRAS*	Bound and stabilized G-quadruplex	Not detected	Inhibited cell proliferation, arrest G2/M phase cell cycle	[140]
TMPyP4	MIA PaCa-2	Intermolecular G-quadruplex	Not detected	Shortened telomeres	Cytotoxicity, arrested cell proliferation, induced anaphase bridges, cellular senescence and apoptosis	[141]

Telomestatin	MIA PaCa-2	Intramolecular G-quadruplex	Not detected	Shortened telomeres	Cytotoxicity, arrested cell proliferation, and induced cellular senescence and apoptosis	[141]
Nitidine	AsPC-1, BxPC-3, MIA PaCa-2, PANC-1	*KRAS*	Bound and stabilized G-quadruplex structure	Downregulated expression of *KRAS*	Cytotoxicity	[142]
4,11-bis(2-Aminoethylamino)anthra[2,3-b]furan-5,10-dione(2a),11-bis(2-aminoethylamino) anthra[2,3b]thiophene-5,10-dione (2b)	PANC-1	*KRAS* mRNA	Bound and stabilized G-quadruplex	Inhibited translation of *KRAS*	Induced apoptosis, inhibited cell growth and colony formation	[143]
Unsymmetrical bisacridines derivatives	PANC-1, MIA PaCa-2, BXpC-3, AsPC-1, Capan-2	Telomere, *c-MYC*, *KRAS*	Bound and stabilized G-quadruplex	Not detected	Inhibited cell proliferation, reduced PANC-1 and MIA PaCa-2 xenograft growth *in vivo*	[144]
Copper(ii) l/d-valine-(1,10-phen) complexes (complex 1a, 1b)	BxPC3, AsPC1	Telomere	Had affinity with G-quadruplex	Not detected	Cytotoxicity	[145]
CX-5461 (Pidnarulex)	MIA PaCa-2, PANC-1	Telomere, *c-MYC*, *c-kit*	Bound with G-quadruplex	Not detected	Inhibited cell proliferation	[146,147]
CX-3543 (Quarfloxin)	MIA PaCa-2	Nucleolin/ribosomal DNA G-quadruplex complexes	Disrupts nucleolin/G-quadruplex complexes on ribosomal DNA	Inhibited rRNA synthesis	Inhibited proliferation, inhibited Pol I transcription, induced apoptosis, decreased tumor growth of MIA PaCa-2 xenografts	[148,149]
Antihelminthic pyrvinium pamoate	PANC-1, Capan-1, HS766T, CFPAC, MIA PaCa-2	Mitochondrial DNA	Bound G-quadruplex	Inhibited transcription of mitochondrial RNA	Inhibited cell viability, mitochondrial pathways, tumor growth of MIA PaCa-2 xenografts	[150]
NSC 317605 and novel indoloquinolines	AsPc1, PANC1, BxPc3, MIA PaCa-2	*c-MYC*, *KRAS*	Bound and stabilized G-quadruplex	Downregulated expression of *KRAS*	Cytotoxicity	[151]
Quinazoline-pyrimidine derivatives	Tumor-naïve pancreatic stellate cells	Telomere, *c-MYC*, *c-kit*, *KRAS*, *BCL-2*	Bound and stabilized G-quadruplex	Not detected	Inhibited tumor growth	[152]
hnRNPA1 and integrinlinked kinase	AsPC-1, PANC-1, MIA PaCa-2, Capan-2	*KRAS*	Destabilized G-quadruplex	Stimulated transcription of *KRAS*	Promoted KRAS-E2F1-ILK-hnRNPA1 circuitry, tumor growth and aggressive phenotypes	[153-155]
Poly [ADP-ribose] polymerase 1	PANC-1	*KRAS*	Destabilized G-quadruplex	Stimulated transcription of *KRAS*	Activated a ROS-G-quadruplex-PARP-1 axis	[156]
Apurinic/apyrimidinic endonuclease 1	PANC-1, BxPc3, MIA PaCa-2	*KRAS*	Bound and stabilized G-quadruplex	Upregulated expression of *KRAS*	Did not sensitize pancreatic cancer cells to chemotherapeutic drugs *in vitro* and *in vivo*	[157]
Polypurine reverse Hoogsteen hairpins	AsPc-1, MIA PaCa-2	*KRAS*, *c-MYC*	Bound and stabilized G-quadruplex	Inhibited transcription of *KRAS* and *c-MYC*	Inhibited cell proliferation	[158,159]

hPOT1: Human protection of telomeres 1; ILK: Integrinlinked kinase; BCL-2: B-cell lymphoma 2; KRAS: Kirsten rat sarcoma viral oncogene homologue; HSP90: Heat shock protein 90; hTERT: Human telomerase reverse transcriptase; NRAS: Neuroblastoma RAS viral oncogene homolog; ROS: Reactive oxygen species.

effects in HGC-27 cells by interacting with *c-kit* promoter G-quadruplexes and inhibiting gene transcription, while a 1,10-phenanthroline derivative causes DNA damage, telomere dysfunction, autophagy, and antitumor effects in AGS cells by stabilizing telomere, *c-kit* and *BCL-2* G-quadruplexes[169-171]. Use of G-quadruplex antibody confirmed that the targeting regulation could help suppress GC[172]. All details are described in Table 4.

Table 3 Overviews of investigations on the effects of small molecule ligands or biomolecules based on G-quadruplex targets in hepatocellular carcinoma

Ligands/biomolecules	Cell lines	Targeting gene/G-quadruplex	Effects on G-quadruplex	Effects on genes	Anticancer phenotypes	Ref.
Platinum(II) complexes with tridentate ligands	HepG2	*c-MYC*	Bound and stabilized G-quadruplex	Inhibited *c-MYC* expression	Cytotoxicity	[160]
Prolinamide derivatives containing triazole	HepG2	*c-MYC*	Bound and stabilized G-quadruplex	Inhibited *c-MYC* expression	Cytotoxicity	[161]
A series of novel 9-O-substituted-13-octylberberine derivatives	HepG2, Sk-Hep-1, Huh-7	*c-MYC*	Bound and stabilized G-quadruplex	Not detected	Cytotoxicity, blocked cell cycle, induced apoptosis, inhibited tumor growth of H22 xenografts	[162]
Series of novel 9-N-substituted-13-alkylberberine derivatives	HepG2, Sk-Hep-1, Huh-7, Hep3	*c-MYC*	Bound and stabilized G-quadruplex	Not detected	Cytotoxicity, blocked cell cycle, induced apoptosis, inhibited tumor growth of H22 xenografts	[163]
Thiazole orange derivatives	HepG2	Telomere	Bound and stabilized G-quadruplex	Not detected	Cytotoxicity	[164]
Peptidomimetic ligands	HepG2	*c-kit1*	Had high affinity with G-quadruplex	Not detected	Inhibited cell proliferation, induced apoptosis	[165]
A 7, 11-disubstituted quinazoline derivative HZ-6d	HepG2, SMMC-7721	*HERC5*	Bound and stabilized G-quadruplex	Inhibited *HERC5* expression	Inhibited cell growth, migration, induced apoptosis, suppressed tumor growth of SMMC-7721 xenografts	[166]
DDX5	HepG2, Huh7, Snu387, Snu423, HepaRG, HepAD38	*STAT1* mRNA	Unwound G-quadruplex	Promoted translation of *STAT1*	Upregulated expression of STAT1 and enhanced IFN-α mediated antiviral effects	[167]
Nucleolin	Huh7.5.1, Huh7.5	Viral core RNA, G-quadruplex	Directly interacted with G-quadruplex	Inhibited viral RNA replication	Suppressed wild-type viral replication and expression	[168]

IFN: Interferon.

Colorectal cancer: Colorectal cancer (CRC) is a digestive tract disease with high morbidity and mortality. *KRAS* mutations are present in about 50% of CRC patients. Gene-targeted therapy is a promising direction for treating CRC. Currently, the potential G-quadruplex gene targets being studied in CRC include telomere, *c-MYC*, *KRAS* and *c-kit*. For the telomeric G-quadruplex ligands, BRACO-19 leads to rapid growth inhibition of flavopiridol-resistant cells[173]; 3,11-difluoro-6,8,13-trimethyl-8H-quino[4,3,2-kl]-acridinium methosulfate (RHPS4), as well as RHPS4-derivatives, induces DNA damage and antiproliferative activity, stabilizes topoisomerase (TOPO) I, and displays cytotoxic and synergistic anticancer effects with TOPO1 inhibitors in CRC cell lines[174-177]. A series of anthracene derivatives substituted with one or two 4,5-dihydro-1H-imidazol-2-yl-hydrazonic groups stabilize G-quadruplexes to different degrees, inhibit telomerase activity, and mediate cytotoxicity[178]. EMICORON cause telomere damage and block cell proliferation and tumor growth of a patient-derived tumor xenograft model[179,180]. Chromene derivatives, the binders of TERRA G-quadruplexes, have cytotoxic effects in HT29 cells[181]. For the ligands targeting *c-MYC* G-quadruplexes, TMPyP4-mediated stabilization of the mutated G-quadruplex reinstate *c-MYC* G-quadruplex structure and inhibit its gene expression[182]. CX3543 (quarfoxin) exhibit proapoptotic and antiproliferative effects by downregulating *c-MYC* and *CCAT1* expression levels *in vivo* and *in vitro*[183]. CX-5461 (pidnarulex) induces DNA damage and inhibits tumor growth *in vivo* by binding to telomere, *c-MYC* and *c-kit* G-quadruplexes[184]. Dihydrochelerythrine and its derivatives improve the stability of *c-MYC* and *c-kit* G-quadruplexes and inhibit HCT116 cell proliferation[185]. Unsymmetrical bisacridines derivatives stabilize *c-MYC* and *KRAS* G-quadruplexes and induce cytotoxicity, apoptosis and senescence in HCT116 cells [144,186]. Additionally, the ligands 7-carboxylate indolo[3,2-b] quinoline tri-alkylamine derivatives targeting *KRAS* and *HSP90A* promoter G-quadruplexes also show anti-CRC activity by decreasing *KRAS* and *HSP90A* expression levels[187]. 3-[2-(Diethylamino)ethyl]-12-methyl-6-oxo-2,3,6,12-tetrahydro-1Hbenzo[4,5]imidazo [1,2-a] imidazo[1′,2′:1,6]pyrido[2,3-d]pyrimidin-14-ium bromide inhibits cell proliferation by interacting with *KRAS* G-quadruplexes[188]. In addition to those common cancer-related genes, G-quadruplexes of other functional genes have been shown on anticancer drug research and development. A naphthalene diimides compound T5 was shown to inhibit CRC cell growth by decreasing

Table 4 Overviews of investigations on the effects of small molecule ligands or biomolecules based on G-quadruplex targets in gastric cancer

Ligands/biomolecules	Cell lines	Targeting gene/G-quadruplex	Effects on G-quadruplex	Effects on genes	Anticancer phenotypes	Ref.
Benzo[a]phenoxazines	HGC-27	*c-kit*	Bound with G-quadruplex	Inhibited *c-MYC* transcription	Cytotoxicity	[169]
Quinazolone derivatives	HGC-27	*c-kit*	Stabilized G-quadruplex	Inhibited *c-kit* transcription	Cytotoxicity	[170]
3-(4-(1H-imidazo[4,5-f][1,10]phenanthrolin-2-yl)-3-(ptolyl)-1Hpyrazol-1-yl)-N,N-dimethylpropan-1-amine (13d)	AGS	Telomere, *c-kit*, *BCL-2*	Stabilized G-quadruplex	Induced telomere dysfunction, DNA damage response	Inhibited cell proliferation, migration, and invasion, promoted cell apoptosis and autophagy by blocking the Akt/mTOR pathway	[171]
G-quadruplex antibody	AGS	G-quadruplex	Not detected	Inhibited transcription of *hTERT* and *BCL-2*	Inhibited cell proliferation, migration, invasion and expression of hTERT and BCL-2, induced apoptosis, blocked cell cycle	[172]

BCL-2: B-cell lymphoma 2; hTERT: Human telomerase reverse transcriptase; mTOR: Mammalian/mechanistic target of rapamycin.

RNA polymerase I (Pol I)-mediated transcription by targeting ribosomal DNA G-quadruplexes[189]. Thiosugar naphthalene diimide conjugates exhibit cytotoxic effects by targeting telomere, *c-MYC* and *KRAS* G-quadruplexes[190]. The natural product gallic acid was found to selectively recognize and stabilize G-quadruplexes of rDNA and *c-MYC*, inhibit their associated mRNA expression, and subsequently suppress tumor growth *in vitro* and *in vivo*[191].

The functional protein or oligonucleotide molecules regulating CRC progression based on special G-quadruplexes have also been explored. For example, hnRNPA1 destabilizes *TRA2B* promoter G-quadruplexes and stimulates its mRNA and protein expression levels, which facilitates proliferation of HCT116 cells[192]. Small nuclear ribonucleoprotein polypeptide A consistently modulates translation of *BAG-1* and inhibits HCT116 cell proliferation[193,194]. PPRHs induces *c-MYC* G-quadruplexes and inhibits proliferation of SW480 cells[159].

The LMNAV6 promoter region forms multiple G-quadruplexes, which increases its transcriptional activity, promotes Lamin A/C protein expression, and induces CRC cell proliferation[195]. FLJ39051, a highly expressed long noncoding RNA in CRC, contains G-quadruplexes. It combines with the RNA helicase DHX36 and promotes CRC cell migration [196]. At present, small molecular ligands or proteins targeting LMNAV6 and FLJ39051 G-quadruplexes have not been reported. All details are described in Table 5.

Gastrointestinal stromal tumors: Gastrointestinal stromal tumors (GISTs) are soft tissue sarcomas originating from Cajal interstitial cells. They mostly frequently occur in the stomach, small intestine, and colorectum, but rarely occur in the esophagus, mesentery, omentum and retroperitoneum. GISTs are characterized by aberrant expression of *c-kit* oncogene, CD117 and CD34. The kinase inhibitor imatinib is an effective drug, but resistance to imatinib induced by active-site mutations has become a practical challenge that cannot be fully addressed by second and third-generation inhibitors. There are two G-quadruplex-forming sequences (*c-kit1* positioned between -12 and -33 bp, *c-kit2* positioned between -64 and -83 bp) upstream of the transcription initiation sites of the human *c-kit* promoter. There are also potential binding sites for transcription factors SP1 and AP2, providing an opportunity for *c-kit*-targeted therapy. A series of 6-substituted indenoisoquinolines and N,N'-Bis[2-(pyrrolidin-1-yl)ethylamino]-2,6-bis[2-(pyrrolidin-1-yl)ethylamino]-1,4,5,8-naphthalenetetracarboxylic acid diimide have been confirmed to stabilize *c-kit* promoter G-quadruplexes, mediate cytotoxicity, and downregulate c-kit protein expression levels in GIST cell lines[197,198]. The latter can also stabilize *BCL-2* promoter and mRNA G-quadruplexes to promote cytotoxicity and inhibit BCL-2 protein expression[198]. All details are described in Table 6.

In summary, targeting G-quadruplexes of cancer-related genes in cancer cells and inducing cytotoxic effects by regulating gene transcription may be an effective strategy for preventing and treating various gastrointestinal cancers. An overview of the advancement of potential drugs that target G-quadruplexes in gastrointestinal cancers is shown as Figure 2.

Application of G-quadruplex in the treatment of gastrointestinal cancers

As anticancer agents: In addition to acting as a target of ligands or proteins, G-quadruplexes can serve as anticancer agents. They can recognize specific biomacromolecules with a high degree of specificity, regulate their biological function, and interfere with cancer progression. The G-quadruplex formed by the G-rich sequence T-22AG can competitively bind to nuclear protein, inhibit its combination with *KRAS* G-quadruplex, and thus inhibit gene transcription and proliferation of Panc-1 cells[199]. AS1411 was an earlier discovered G-quadruplex sequence with antiproliferative activity by targeting nucleolin in a variety of cancer cells, such as PC, GC and CRC[200]. The sequences TBA and its derivatives exhibit antiproliferative effects in HCT 116p53$^{-/-}$ cells *via* the G-quadruplex structure; the target of which may be uL3

Table 5 Overviews of investigations on the effects of small molecule ligands or biomolecules based on G-quadruplex targets in colorectal cancer

Ligands/biomolecules	Cell lines	Targeting gene/G-quadruplex	Effects on G-quadruplex	Effects on genes	Anticancer phenotypes	Ref.
BRACO-19	HCT116, Flavopiridol-resistant HCT116	Telomere	Stabilized G-quadruplex	Not detected	Rapid inhibition of cell growth	[173]
RHPS4 (3,11-difluoro-6,8,13-trimethyl-8H-quino[4,3,2-kl]acridinium methosulfate) and RHPS4-derivatives	HT29, HCT116	Telomere	Bound with G-quadruplex	Induced DNA damage	Stabilized TOPO1, cytotoxicity, inhibited cell proliferation, had synergistic anticancer effects with TOPO1 inhibitors	[174-177]
A series of anthracene derivatives substituted with one or two 4,5-dihydro-1H-imidazol-2-yl-hydrazonic groups	LoVo	Telomere	Induced G-quadruplex structures, bound and stabilized G-quadruplex	Induced DNA damage	Cytotoxicity, telomerase inhibition	[178]
EMICORON	HT29, HCT116, A90 colon epithelial tumor cell line	Telomere	Bound with G-quadruplex	Increased telomere damage	Cytotoxicity, inhibited cell proliferation and tumor growth of patient-derived tumor xenograft	[179, 180]
Chromene derivatives	HT29	*Telomere* RNA	Bound with G-quadruplex	Not detected	Cytotoxicity	[181]
TMPyP4	SW480, SW620	*c-MYC*	Stabilized the mutated G-quadruplex structure	Inhibited *c-MYC* expression	Silenced *c-MYC* expression	[182]
CX-3543 (quarfloxin)	HT29	*c-MYC*	Not detected	Inhibited *c-MYC* expression	Reduced *CCAT1* expression, promoted cell apoptosis, inhibited cell proliferation and tumor growth of HT29 xenografts	[183]
CX-5461 (pidnarulex)	HT-29, DLD-1, CT26	Telomere, *c-MYC*, *c-kit*	Bound with G-quadruplex	Caused DNA damage	Inhibited tumor growth of CT26 xenografts	[184]
Dihydrochelerythrine and its derivatives	HCT116	*c-MYC*, *c-kit*	Stabilized G-quadruplex	Not detected	Inhibited cell proliferation	[185]
Unsymmetrical bisacridines derivatives	HCT116	*c-MYC*, *KRAS*	Bound and stabilized G-quadruplex	Not detected	Induced cytotoxicity, apoptosis and senescence	[144, 186]
7-carboxylate indolo[3,2-b] quinoline tri-alkylamine derivatives	HCT116, SW620	*KRAS*, *HSP90A*	Stabilized G-quadruplex	Decreased *KRAS* and *HSP90* mRNA expression, and *KRAS* transcription	Inhibited cell proliferation and protein expression of KRAS and HSP90A, promoted apoptosis	[187]
	HCT116	*KRAS*	Bound and stabilized G-quadruplex	Decreased *KRAS* mRNA expression	Inhibited cell proliferation	[188]
Naphthalene diimides compound T5	Colorectal cancer cell	rDNA	Had high affinity with G-quadruplex	Impaired RNA Pol I elongation, inhibited Pol I transcription	Inhibited cell growth by inducing a rapid inhibition of Pol I transcription, nucleolus disruption, proteasome-dependent Pol I catalytic subunit A degradation and autophagy	[189]
Thiosugar naphthalene diimide conjugates	HT29	Telomere, *c-MYC*, *KRAS*	Bound and stabilized G-quadruplex	Not detected	Cytotoxicity	[190]
Gallic acid		rDNA, *c-MYC*	Bound and stabilized G-quadruplex	Inhibited expression of rDNA and *c-MYC*	Cytotoxicity, inhibited tumor growth of SW480 xenografts	[191]
HnRNPA1	HCT116	*TRA2B* promoter	Destabilized G-quadruplex	Stimulated *TRA2B* transcription	Promoted cell proliferation and expression of TRA2B	[192]
SNRPA	HCT116	*BAG-1* mRNA	Bound with G-quadruplex	Inhibited translation of *BAG-*	Inhibited cell proliferation	[193, 194]

				1		
PPRHs	SW480	*c-MYC*	Bound and stabilized G-quadruplex	Inhibited transcription of *c-MYC*	Inhibited cell proliferation	[159]

PPRHs: Polypurine reverse Hoogsteen hairpins; TOPO: Topoisomerase; KRAS: Kirsten rat sarcoma viral oncogene homologue; HSP90: Heat shock protein 90.

Table 6 Overview of investigations on the effects of small molecule ligands based on G-quadruplex targets in gastrointestinal stromal tumor

Ligands/biomolecules	Cell lines	Targeting gene/G-quadruplex	Effects on G-quadruplex	Effects on genes	Anticancer phenotypes	Ref.
6-Substituted indenoisoquinolines	GIST882	*c-kit*	Stabilized G-quadruplex	Inhibited *c-kit* transcription	Cytotoxicity, inhibited expression of c-kit protein	[196]
N,N'-Bis(2-(pyrrolidin-1-yl)ethylamino)-2,6-bis(2-(pyrrolidin-1-yl)ethylamino)-1,4,5,8-naphthalenetetracarboxylic acid diimide	GIST882, GIST48, GIST62	*c-kit*, *BCL-2*, *BCL-2* mRNA	Stabilized G-quadruplex	Not detected	Cytotoxicity, inhibited expression of c-kit and BCL-2 proteins	[197, 198]

BCL-2: B-cell lymphoma 2.

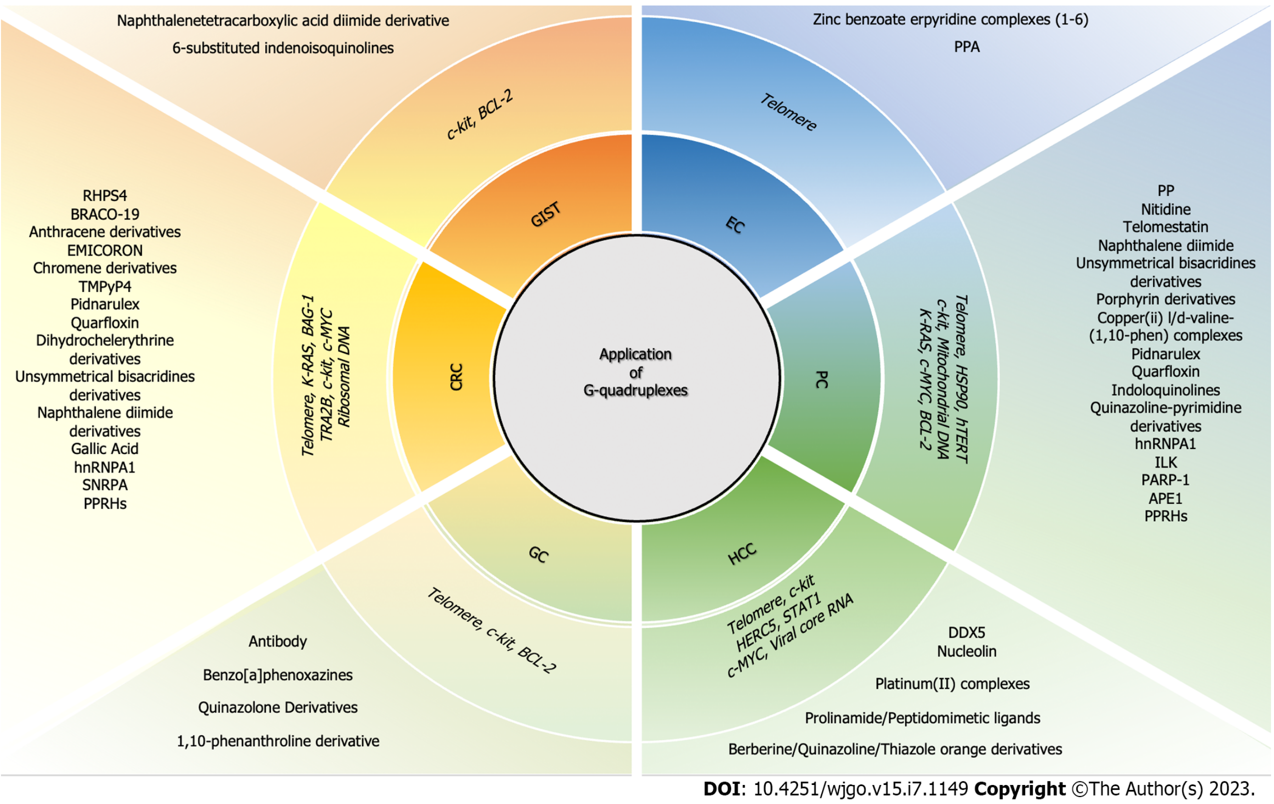

Figure 2 G-quadruplex targets and the targeting small molecule ligands and biomolecules in six gastrointestinal cancer types. EC: Esophageal cancer; PC: Pancreatic cancer; HCC: Hepatocellular carcinoma; GC: Gastric cancer; CRC: Colorectal cancer, GIST: Gastrointestinal stromal tumor; PPA: 2,6-bis[3-(N-Piperidino) propionamido] anthrace-ne-9,10-dione; PP: Antihelminthic pyrvinium pamoate; ILK: Integrinlinked kinase; PARP1: Poly (ADP-ribose) polymerase 1; APE1: Apurinic/apyrimidinic endonuclease 1; PPRHs: Polypurine reverse Hoogsteen hairpins; DDX5: Dead box polypeptide 5; RHPS4: (3,11-difluoro-6,8,13-trimethyl-8H-quino[4,3,2-kl]acridinium methosulfate) and RHPS4-derivatives; SNRPA: Nuclear ribonucleoprotein polypeptide A; BCL-2: B-cell lymphoma 2; TRA2B: Transformer-2 protein homolog beta; KRAS: Kirsten rat sarcoma viral oncogene homologue; HSP90: Heat shock protein 90; hTERT: Human telomerase reverse transcriptase.

[201]. Similarly, the G-quadruplex sequences INT-B (T30175) and its derivatives, along with d(GGGT)$_4$ and its analogs also inhibit HCT 116p53$^{-/-}$ cell proliferation, but the specific target remains unclear[202,203]. All details are described in Table 7.

As an assistant in anticancer agents: G-quadruplex sequences mainly have two functions. In the research and development of anticancer drugs, G-quadruplex sequences were often used as the carriers of drugs or targeted agents in delivery systems to improve the delivery efficiency and targeting of anticancer drugs[204]. The carried molecules have included such chemotherapeutic drugs as paclitaxel, docetaxel, doxorubicin, triptolide, epirubicin, gemcitabine, thymoquinone, TMPyP4 and 5-fluorouracil, targeting cancers like HCC, PC and CRC[205,206]. As an important component of anticancer agents, G-quadruplex sequences can also help produce or improve anticancer efficacy. For example, the G-quadruplex dependent intracellular self-assembly device can continuously produce ROS to enhance antitumor effects of 5-aminolevulinic-acid in EC cells[207]. The parallel G-quadruplex configurations boost the cellular uptake of 5-fluoro-20-deoxyuridine oligomers, which stimulate cytotoxicity in 5-fluorouracil resistant CRC cells[208].

CHALLENGES OF ANTICANCER STRATEGIES BASED ON G-QUADRUPLEX TARGETS

Although many small molecular ligands or biomolecules targeting G-quadruplexes have been found to have anticancer activity *in vitro* and *in vivo*, it is still uncertain whether they can achieve such effects in humans. Unfortunately, many promising drugs have not passed clinical trials in the past, as biological systems are complex and many internal and external factors can affect drug effectiveness. The application of G-quadruplex targets in the treatment of gastrointestinal cancers will also face some challenges.

Dual role of G-quadruplexes in transcriptional and translational regulations

At first, G-quadruplexes were simply described as an obstacle to the transcription of cancer-related genes, leading to increased efforts to design and develop small molecule ligands as anticancer drugs targeting G-quadruplex structure, which attracted widespread attention[209]. However, evidence has shown that G-quadruplexes can regulate gene transcription at multiple levels, including through epigenetic modification and chromatin structure[210]. Because of the complexity of gene expression regulation, G-quadruplexes can play dual roles in gene transcription: Blocking polymerase to inhibit gene transcription; and recruiting transcription factors to promote gene transcription[117]. Under certain conditions, G-quadruplexes can trigger opposing effects on the same target[211]. The regulation of translation by RNA G-quadruplexes also has two sides. G-quadruplexes can prevent ribosome entry under conditions of cap-dependent translation, but can also prompt ribosome entry under conditions of cap-independent translation[212]. With both DNA G-quadruplex-mediated regulation of transcription and RNA G-quadruplex-mediated regulation of translation, the final effects depend on the specific environment. Further research is required to investigate if ligands targeting G-quadruplexes in the tumor microenvironment can result in the predicted anticancer effects and if they can affect normal cells.

Biological factors affecting G-quadruplex formation

Chromatin and DNA modifications: The formation of G-quadruplexes *in vivo* is the result of the comprehensive action of various factors within its cell environment, including chromatin. Although a previous study indicated that transcriptional activation increased the instability of potential G-quadruplex-forming sequences, ChIP-seq research confirmed that promoter G-quadruplex formation preceded transcription rather than depending on transcription. Additionally, chromatin compaction led to a loss of RNA polymerase II (Pol II) and promoter G-quadruplexes[213]. Different types of DNA modifications can directly influence the formation of G-quadruplexes. For example, the stability and kinetic associations of G-quadruplex structures were increased by cytosine methylation (in addition with 5mC), which did not directly act on the Hoogsteen bonding[214]. Guanine bases in nucleic acids can be oxidized to 8-oxo-7,8-dihydroguanine (8-oxoguanine), which can destroy the G-quadruplex structure in cancers[215]. Oncogene promoter regions are prone to hypomethylation, while those of tumor suppressor genes are prone to hypermethylation. These factors may indirectly impact the formation of G-quadruplexes and the resulting regulatory effects.

G-quadruplex-binding proteins: G-quadruplexes play various regulatory functions by interacting with proteins. G-quadruplex-binding proteins indirectly participate in biological processes such as DNA replication, gene transcription and telomere maintenance *via* G-quadruplexes. The influence of binding proteins on the formation of G-quadruplexes mainly involves two aspects: Unfolding G-quadruplex structures and stabilizing G-quadruplex structures. Helicases are important binding proteins that can unwind G-quadruplexes and interfere with their regulatory functions. Such proteins are mainly classified as canonical helicases, including the RecQ-like and DEAD box or DEAH box helicase families. *In vitro*, these three helicases have been reported to bind to the 3′ tail of the DNA substrate and subsequently repetitively catalyze 3′-5′ unfolding of G-quadruplexes in an ATP-independent manner[216]. In addition, nonhelicase binding proteins, such as G-rich RNA sequence binding factor 1 and cellular nucleic acid-binding protein, can sequester the unfolded G-quadruplex form[216-218]. In contrast, there are also binding proteins that can support the G-quadruplex structure, such as nucleolin and RNA-binding protein 4[168,219]. Additionally, RNA-binding proteins are important influencing factors of RNA G-quadruplexes. G-quadruplex-binding proteins are also potential targets for cancer treatment because their effects contribute to G-quadruplex functions[220]. Significantly, the specific effects of these binding proteins on the targeted G-quadruplexes depend on their specific intracellular environments.

Table 7 G-quadruplexes as anticancer agents

Tumor model	G-quadruplex name	Sequence (5'-3')	Protein target	Cells	Anticancer phenotype	Ref.
Pancreatic cancer	*T-22AG*	GGAGGGGGAGAAGGGAGAAGGG	Nuclear protein	Panc-1	Reduces cell growth	[199]
	AS1411	GGTGGTGGTGGTTGTGGTGGTGGTGG	Nucleolin	PANC-1	Inhibited cell proliferation	[200]
Gastric cancer	*AS1411*	GGTGGTGGTGGTTGTGGTGGTGGTGG	Nucleolin	KATOIIIe, HGC27	Inhibited cell proliferation	[200]
Colorectal cancer	*AS1411*	GGTGGTGGTGGTTGTGGTGGTGGTGG	Nucleolin	HCC 2998, HT-29, KM12, HCT-116, SW620, HCT-15, LS174T	Inhibited cell proliferation	[200]
	TBA	GGTTGGTGTGGTTGG	uL3	HCT 116p53$^{-/-}$	Impaired ribosomal RNA processing, leading to the accumulation of pre-ribosomal RNAs, arrested cells in the G2/M phase and induced early apoptosis	[201]
	L-TBA	GGTTGGTGTGGTTGG				
	LQ1	GGTTGGTGTGGTTGG				
	LQ2	GGTTGGGTGTGGTTGG				
	LQ3	GGTTGGGTGTGGTTGG				
	INT-B (T30175)	GTGGTGGGTGGGTGGGT	Not detected	HCT 116p53$^{-/-}$	Inhibited cell proliferation	[202]
	INT-BS2	GSGGTGGGTGGGTGGGT				
	INT-BS5	GTGGSGGGTGGGTGGGT				
	INT-BS9	GTGGTGGGSGGGTGGGT				
	INT-BS13	GTGGTGGGTGGGSGGGT				
	INT-BS17	GTGGTGGGTGGGTGGGS				
	TT-INT-B	TTGTGGTGGGTGGGTGGGT				
	Qnat	GGGTGGGTGGGTGGGT	Not detected	HCT 116p53$^{-/-}$	Inhibited cell proliferation	[203]
	QS4	GGGSGGGTGGGTGGGT				
	QS8	GGGTGGGSGGGTGGGT				
	QS12	GGGTGGGTGGGSGGGT				
	QS16	GGGTGGGTGGGTGGGS				

Inflammatory cytokines: Inflammatory cytokines produced during inflammation reactions can support the production of ROS and nitrogen species (RONS), which may cause DNA damage. RONS can remove an electron from DNA bases and generate an electron hole, then transfer it to a base with a lower ionization potential. Guanine has the lowest ionization energy among the four DNA bases, making it particularly vulnerable to oxidative damage[221]. The most significant oxidative damage involves hydroxyl free radicals interacting with guanine to induce 8-oxoguanine, which can pair with adenine bases, and induce a G>T conversion during replication[3]. The degree of DNA damage depends on the position of the oxidized guanines and G-quartets.

Lack of selectivity of G-quadruplex ligands

At present, the design of small molecules is mainly based on the specific G-quadruplex configurations. As mentioned previously, there are three basic configurations for G-quadruplexes, and different nucleic acid sequences may form the same G-quadruplex configuration. Therefore, one small molecule ligand may have similar binding stabilities with the G-quadruplex structures of different genes, which may reduce the targeting of gene therapy. For example, berberine can combine with the parallel structures of the *KRAS* and *c-MYC* promoters[6,16]. This inhibits *KRAS* and *c-MYC* expression and induces cytotoxicity in various cancer cells that express these oncogenes. Further work is needed to determine if this drug can cause negative effects in normal cells.

PROSPECTS

G-quadruplexes are widely distributed throughout the human genome and are key aspects of gene transcription and translation regulation. Therefore, G-quadruplexes can be the drug targets against multiple human diseases, such as viral infection[222], bacterial infection[223], muscular atrophy[60] and cancer, especially gastrointestinal cancers. However, there are some uncertainties with this application that should be explored further. Firstly, G-quadruplex-mediated regulation of transcription and translation in gastrointestinal tissues require more investigation, especially during tumorigenesis. The development of high-throughput sequencing and single nucleotide polymorphism detection may provide new opportunities to establish specific gene therapy strategies for gastrointestinal cancers based on G-quadruplexes. Secondly, the transcriptional activation function of G-quadruplexes is needed in some normal physiological processes, raising the concern that anticancer therapies targeting G-quadruplexes may interfere with normal cellular activities. Fully understanding the roles of G-quadruplexes in different biological processes, especially in various diseases, is helpful for addressing this challenge. Thirdly, G-quadruplexes can both inhibit and promote gene transcription and translation, with the final effects depending on the intracellular environment. This ultimately directly affects the treatment outcome. With the progress of molecular diagnosis technology, it may be necessary to specifically evaluate the patient's internal environment before treatment. Fourthly, small molecule ligands and biomolecules may simultaneously target genes with the same G-quadruplex configurations, resulting in a need for improved selectivity or targeting. Fifthly, the formation of a G-quadruplex is affected by a variety of biological factors. Whether these factors can interfere with a G-quadruplex-targeted therapy requires further study. Sixthly, clinical trials are needed to verify the efficacy of such small molecule ligands and biomolecules.

CONCLUSION

In addition to telomeres, G-quadruplexes are widely present in the promoter regions of oncogenes as well as cancerous genes, and can regulate various biological processes, especially gene transcription and translation, laying a good foundation for G-quadruplexes to become anticancer targets from the perspective of gene regulation. Multiple genes regulating EC, PC, HCC, GC, CRC and GIST have been found to contain G-quadruplex structures, including the key regulatory gene *KRAS* for PC and CRC, and *c-kit* for GC and GIST. Many small molecular ligands or biomolecules based on the G-quadruplex of these genes have been designed, synthesized, or discovered, and preclinical studies have shown that these molecules have good anticancer effects. Therefore, G-quadruplexes as targets against gastrointestinal cancers have broad application prospects. However, due to the diversity of G-quadruplex functions and the complexity of the biological internal environment, the application of G-quadruplex as a target of anticancer drugs still faces some challenges, which requires further exploration and research. We hope this work will provide references for anticancer strategies based on G-quadruplex targets in gastrointestinal cancers.

FOOTNOTES

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