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REVIEW

G-Quadruplex Structure: a Target for Anticancer Therapy and a Probe for Detection of Potassium

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Abstract—G-Quadruplexes are four-stranded DNA structures that play important regulatory roles in the maintenance of telomere length by inhibiting telomerase activity. Telomeres are specialized functional DNA–protein structures consisting of a variable number of tandem G-rich repeats together with a group of specific proteins. Telomere losses during cell replication are compensated by telomerase, which adds telomeric repeats onto the chromosome ends in the presence of its substrate—the 3′-overhang. Recently, quadruplexes have been considered as a potential therapeutic target for human cancer because they can inhibit telomerase activity, and some quadruplex-interacting drugs can induce senescence and apoptosis of cancer cells. In addition, due to the potassium preference to the other cations, especially sodium ions, quadruplexes have been suggested for developing potassium detection probes with higher sensitivity and selectivity. This review will illustrate these two aspects to provide further understanding of G-quadruplex structures.

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Key words: G-quadruplex, G-quadruplex-interacting ligand, telomere, telomerase, FRET, potassium detection

DNA is usually regarded as a duplex molecule in which two self-complementary strands are held together by Watson–Crick base pairs. However, certain DNA sequences that are guanine rich can form four-stranded structures called G-quadruplexes under certain cation conditions [1-4]. These structures have been confirmed in chromosome ends [5], thrombin-binding aptamer (TBA) [6], immunoglobulin switch regions [7, 8], gene transcriptional regulatory regions, e.g. the insulin gene [9], and also the promoter of certain oncogenes, such as c-MYC and BCL2 [10-12]. Some synthesized G-rich oligonucleotides can also form G-quadruplex *in vitro* as confirmed by NMR spectroscopy [13, 14], X-ray crystallography [15, 16], and CD spectroscopy [17, 18]. Recently, G-quadruplexes frequently reported in telomeric repeat sequences have been regarded as a target for inhibiting telomerase activity and a probe for detecting potassium concentration under physiological conditions due to their relatively high selectivity and sensitivity.

Abbreviations: CCP) cationic conjugated polymer; FRET) fluorescence resonance energy transfer; PSO) potassium sensing oligonucleotides; TBA) thrombin-binding aptamer.

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GENERAL PROPERTIES OF G-QUADRUPLEX STRUCTURE

G-Tetrad. The building block of G-quadruplexes is G-tetrad, also called G-quartet [19], which arises from the association of four nearly coplanar guanines linked with eight Hoogsteen hydrogen bonds (Fig. 1). Each guanine shows an *anti*- or *syn*-conformation according to its glycosidic bond orientation [20] and makes two hydrogen bonds with its neighbor (N1 to O6 and N2 to N7). More than two tetrads stack on top of each other by π-π interaction to form a quadruple-helical structure.

G-Quadruplex topologies. Although the basic building block is similar, different quadruplex structures are formed according to the strand stoichiometry, strand orientation, guanine glycosidic torsion angle, connecting loops, and the metal coordination [13, 21]. DNA can form quadruplex structures either through the folding of a single G-rich strand or the association of two or four G-rich strands: a single G-rich strand could form an intramolecular basket-type structure or an intramolecular chair-type structure [22], and under certain conditions a propeller-type structure (Fig. 2). Quadruplexes formed with two strands have relatively complicated and irregular

structures [22]. The four-strand quadruplex constructs a parallel structure with all strands located in the same direction, and the guanines all show *anti*-modes demonstrating that this structure is favored without looping constraints. Depending on strand orientation, two types of quadruplexes are designated: parallel structure with four strands showing the same orientation, and antiparallel structure with at least one G-tract antiparallel to the others. Parallel quadruplexes have all guanine glycosidic angles in an *anti*-conformation, while antiparallel quadruplexes have both *syn*- and *anti*-guanines arranged in a way that is particular for a given topology [23]. The sequences that link the two neighboring G-tetrads forms three kinds of loops in G-quadruplex structures: edgewise loops or so-called lateral loops connecting two adjacent G-tracts; diagonal loops connecting two opposing antiparallel strands; and double-chain-reversal loops (sometimes termed propeller type loops) connecting two adjacent G-tetrad planes [24-26]. As the four G-tract fold together to form a G-quadruplex structure, the four sugar-phosphate chains project away from the tetrad and create four grooves which have different dimensions depending on the quadruplex geometry and the nature of the grooves: quadruplexes constructed of four parallel strands have four equivalent grooves [27, 28]; quadruplexes formed with alternating *anti-syn-anti-syn* dG within each quartet have two narrow and two wide grooves [6]; moreover, quadruplexes formed with *anti-anti-syn-syn* alternation within each quartet have one wide, one narrow and two medium width grooves [29]. Grooves in quadruplexes with only lateral or diagonal loops are relatively simple with no steric interaction of loop sequences. In contrast, grooves

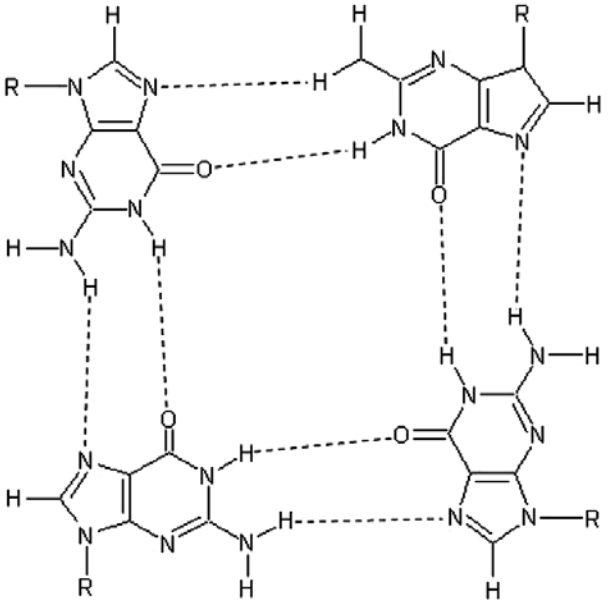


Fig. 1. Arrangement of guanines in a G-tetrad. Each G forms two Hoogsteen hydrogen bonds (dotted lines) with its neighboring counterpart.

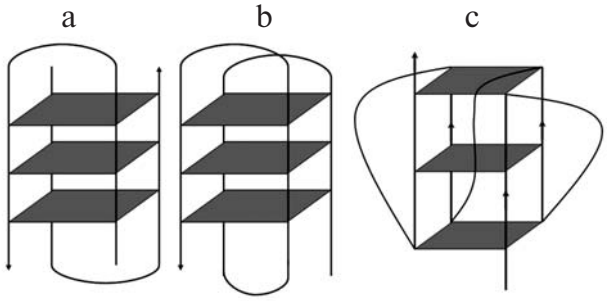


Fig. 2. Diagrams of intramolecular G-quadruplex structure: a) an intramolecular chair-type quadruplex model, which contains complicated parallel/antiparallel G-tracts and three lateral loops; b) an intramolecular basket-type quadruplex model with complicated parallel/antiparallel G-tracts and three loops, one diagonal loop and two lateral loops; c) an intramolecular propeller-type quadruplex model. All the four G-tracts orient in the same direction linked by three double-chain-reversal loops.

in quadruplexes with double-chain-reversal loops show more complicated structures because of the insertion of the variable-sequence loops into the grooves.

G-Quadruplexes formed in telomeric repeat sequences. Many studies have been conducted on the quadruplex topological structures formed in the human telomeric repeat sequences under Na^+ and K^+ conditions because they showed the ability to inhibit telomerase, and thus could be an efficient method for inhibiting telomerase activity and providing important information for drug targeting of G-quadruplexes in human telomeres. In the structure analysis of human telomeric sequences d[AGGG(TTAGGG)$_3$] (Tel22), a single stable basket-type intramolecular quadruplex structure was formed in the presence of Na^+ [26, 30]. In this intramolecular structure, all the three stacked G-tetrads with *anti-anti-syn-syn* glycosidic conformations around each G-tetrad, and three TTA loops adopt successive lateral, diagonal, and lateral alignments, so that each of the strands has both parallel and antiparallel adjacent strands. In 2002, a crystal structure was reported under K^+ conditions on the same sequence with all four G-tracts oriented in the same direction and three linking loops (double-chain-reversal loops) positioned on the exterior of the quadruplex core in the propeller-like arrangement [26]. In 2005, Phan et al. reported that three-repeat human telomere sequences form a bimolecular (3 + 1) quadruplex in Na^+ solutions. In this G-quadruplex assembly, there are one *syn-syn-syn-anti* and two *anti-anti-anti-syn* G-tetrads, two lateral loops, three G-tracts oriented in one direction, and the fourth oriented in the opposite direction [31]. Later they reported an additional two kinds of intramolecular quadruplexes of the (3 + 1)-type under K^+ conditions formed by four-repeat telomeric repeat sequences [32]: both structures have one double-reversal and two lateral loops, but they differ in the successive order of loop arrangements as the 3′-flanking sequences of these two

strands are different, which is critical for the formation of G-quadruplexes in the presence of K^+. Recently, Yang and coworkers reported a different intramolecular G-quadruplex folding topology with hybrid-type mixed parallel/antiparallel strands in Tel26 [33]. It also contains three G-tetrads with mixed guanine arrangements that are consecutively connected with a double-chain-reversal loop and two lateral loops with each consisting of three TTA sequences. Unlike the (3 + 1)-type reported by Phan et al., in this structure the first, second, and fourth G-strands are parallel to each other, while the third strand is antiparallel with the other three strands.

G-QUADRUPLEX: A TARGET FOR ANTICANCER THERAPY

Telomere, telomerase, and cancer. The telomere, a complex of G-rich sequences and associated proteins, protects eukaryotic chromosome ends from genome degradation, end-to-end chromosomal fusion, and DNA rearrangement. Telomeric DNA formed by short G-rich repeat sequences (in mammals TTAGGG, it plants TTTAGGG) varies in length in all eukaryotes from 5 to 20 kb, according to age, organ, and the proliferative history of cell lines [34, 35]. As revealed in the "end replication problem" telomeres shorten 30-200 bp per replication cycle, and about 60-70 cycles later cells enter into a state in which telomeres are recognized as damaged DNA, leading to p53-dependent apoptosis, arrested proliferation, senescence, short life span, or genomic instability [36].

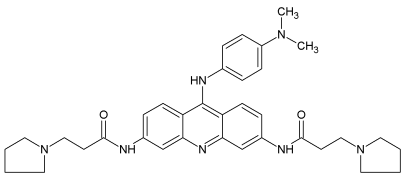
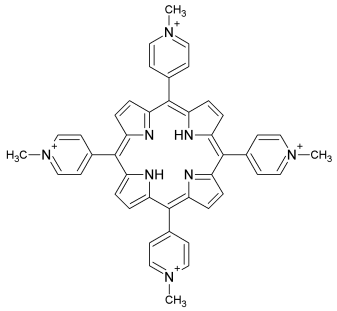
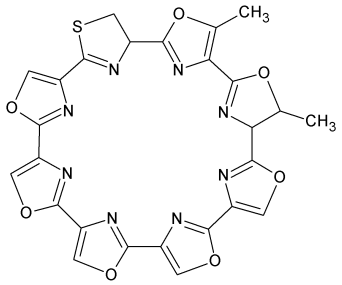
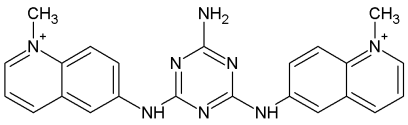
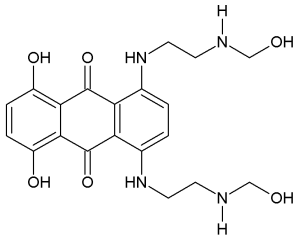
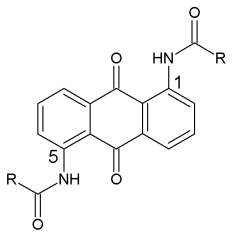
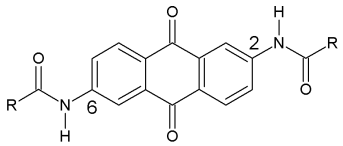
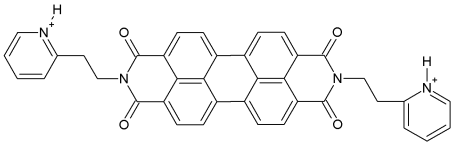
Telomerase, a reverse transcriptase, consisting of template RNA (TER) and telomerase repeat transcript subunit (TERT), can add telomere repeats onto chromosome ends on the basis of its internal RNA template [37]. It has been the focus of intense study as its up-regulation has been detected in approximately 85% of more than 3000 human malignant tumor biopsies, including the most common cancers, such as breast cancer, prostate cancer, lung cancer, liver cancer, pancreatic cancer, and colon cancer [38, 39]. However, in somatic tissues no telomerase activity has been confirmed. Therefore, the evidence indicates that telomerase inhibition could provide a useful strategy for curing cancer. The key problem of direct telomerase inhibition is that a time-lag is required before telomeres reach the critically short length that triggers senescence and apoptosis. Thus, it is proposed that telomerase inhibitors could work with other chemotherapeutic agents that can kill cancer cells. These ligands, which can promote and stabilize G-quadruplex, a structure formed by the telomere 3′-overhang folding back of itself, are thought to inhibit telomerase by blocking its access to its substrates.

G-Quadruplex interacting ligands. Ligands designed to stabilize G-quadruplex structure are derivatives of acridines, cationic porphyrins, triazines, anthraquinones, and perylenes (table). These compounds are expected to stabilize the G-quadruplex structure by binding to the G-quartet on either one end or both ends of the quadruplex and therefore block the access of telomerase to the G-overhang and also cause the disassociation of telomere binding proteins with subsequent apoptosis [40]. Since all these compounds are based on or derived from duplex intercalators, low selectivities are triggered for quadruplexes against duplex DNA, thus leading to inevitable nonspecific cytotoxicity [41, 42]. But that mechanism could be of great importance for designing drugs that are highly specific to the quadruplexes formed in telomeric repeat sequences and may facilitate producing drugs with less or even no cytotoxicity for curing cancer. To date some compounds binding to the grooves of G-quadruplex have been developed, such as carbocyanine dyes DODC and a bifuryl compound DB832 [43-45], providing attractive strategies for developing drugs that can specifically bind G-quadruplex against duplex DNA as the groove geometry is unique between duplex DNA and G-quadruplex structures, and also the groove dimension between the quadruplexes is variable according to G-quadruplex type. These quadruplex groove-binding drugs could be one of the future directions for anticancer drug design due to their high selectivity toward quadruplex DNA against duplex DNA.

BRACO-19. With three of their rings substituted by groups that can interact with the grooves of G-quadruplex structures, acridine compounds have been promising agents for further investigation. A substituted acridine compound, 3,6,9-trisubstituted BRACO-19, has been reported to have potent and selective activity against telomerase, yet with up to 20-fold less short-term cytotoxicity [46, 47]. In addition, BRACO-19 inhibited cell growth inhibition by 96% together with loss of nuclear hTERT expression, and also increase in atypical mitoses and chromosomal fusions, which are indicative of telomere dysfunction [48]. Compared with other drugs, a major advantage of BRACO-19 is avoidance of acute nonspecific cytotoxicity at equivalent concentrations required to completely inhibit telomerase activity, because only a short-term lag is needed before the occurrence of antitumor effects. This suggests that BRACO-19 is not acting as a mere telomerase inhibitor.

TMPyP4. The tetra-(*N*-methyl-4-pyridyl)porphyrin (TMPyP4), a kind of porphyrin compound, has been reported to show a remarkable inhibiting effect on telomerase activity [42, 45, 49]. With its porphyrin ring stacking on the G-tetrad and each of the cationic N-methylpyridine groups intercalating into each of the four grooves of the quadruplex, TMPyP4 preferentially facilitates the formation of intermolecular G-quadruplex structures [50]. It caused a 50% inhibition of telomerase activity in HeLa cell-free extract at concentrations in the range ≤50 μM [51], triggered telomerase inhibition and

G-Quadruplex interacting ligands

BRACO-19	$C_{35}H_{43}N_7O_2$	
TMPyP4	$C_{44}H_{38}N_8$	
Telomestatin	$C_{26}H_{15}SO_7$	
12459	$C_{23}H_{22}N_8$	
Mitoxantrone	$C_{20}H_{26}N_4O_6$	
1,5-Diaminoanthraquinone	$C_{16}H_8N_2O_4R_2$	
2,6-Diaminoanthraquinone	$C_{16}H_8N_2O_4R_2$	
PIPER	$C_{38}H_{26}N_4O_4$	

cell growth arrest in G_2-M phase in MCF7 cells [52], resulted in down-regulation of hTERT and c-MYC expression in human tumor cells [53, 54], and induced anaphase bridges in sea urchin embryos [55]. These demonstrated that cationic porphyrin TMPyP4 functioned in antitumor therapy through inhibiting telomerase activity or arresting the cells in mitosis.

Telomestatin. Telomestatin, a natural G-quadruplex-interacting compound isolated from *Streptomyces anulatus* 3533-SV4 [56] with a 70-fold selectivity towards intramolecular quadruplex against duplex DNA, is an attractive agent for anticancer therapy [42, 50, 57, 58]. In human EcR293 cells, telomestatin treatment impaired the conformation and the length of the telomeric G-overhang, inhibited POT1 to the telomeric G-overhang, and completely dissociated TRF2 from telomeres [59]. This confirmed that telomestatin can uncap telomere ends, which causes telomeric dysfunction characterized by end-to-end fusion, which is inappropriate recombination, and G-overhang degradation [60, 61]. An interesting result is that after short-term treatment with telomestatin at telomerase-activity inhibiting concentrations, a dose-dependent cytotoxicity and induction of apoptosis in neuroblastoma cells occurred [62]. This might be a breakthrough for anticancer therapy because it does not need a lag period for telomeres to be shortened to critical short length before cell apoptosis and senescence. In neuroblastoma (NB) cells, a correlation between telomerase activity and hTERT mRNA expression was detected after telomestatin treatment, but no significant correlation was shown between telomerase activity and telomere length. This confirmed that alternative lengthening of telomeres (ALT) is a mechanism for telomere maintenance in some cells [63, 64].

Some other drugs. Other drugs stabilizing the quadruplex structure have been tested, including triazine derivatives anthraquinones and perylenes. 2,4,6-Triamino-1,3,5-triazine derivative 12459 has been shown to impair the hTERT splicing pattern through stabilizing the quadruplex located in the 5′ end of intron 6, which contains GGG repeat motifs [65], and trigger time and dose-dependent G-overhang degradation, senescence-like growth arrest, and a short term mitochondrial pathway mediated apoptosis that is independent of the presence of telomerase activity with a characterization of a dysfunction of the BCL-2/Bax balance, caspase 3 and poly(ADP-ribose) polymerase (PARP) cleavage [66]. Mitoxantrone, a synthetic aminoanthraquinone interacting with DNA topoisomerase II showed antitumor activity through inhibiting both DNA replication and DNA-dependent RNA synthesis. Disubstituted amidoanthraquinone could modulate hTERT expression and inhibit telomerase activity. Among these drugs, 1,5- and 2,6-position-substituted anthraquinones are further investigated to explore the effects on cytotoxicity, telomerase inhibition, and hTERT expression [67, 68]. In addition, the perylene based drug PIPER and its modified derivative have been reported to have high selectivity to quadruplexes and inhibit telomerase activity [69].

G-QUADRUPLEX: A PROMISING PROBE FOR PRECISE POTASSIUM DETECTION

Potassium ions play important roles in maintenance of extracellular osmolarity and regulation of the other ions in organisms through the potassium ion channel. They are also essential to the production of electrical signals in nerve systems [70]. Recently, irregular heartbeat was related to K^+ channel binding protein deficiency [71]. Thus, it is necessary to detect the potassium concentration under physiological conditions with high precision. As in living organisms, four elements dominate as free cations; their approximate concentrations are: 145 mM Na^+, 5 mM K^+, 2.5 mM Ca^{2+}, 1.5 mM Mg^{2+}. Precise methods for potassium detection should eliminate the interference of the other ions, especially the high level of Na^+. Based on fluorescence resonance energy transfer (FRET) and potassium sensing oligonucleotides (PSO) which can form G-quadruplexes structure under potassium ion conditions, some probes with high selectivity and sensitivity for K^+ detection have been designed [72-77]. The principle of this technique lies in the fact that potassium ion binds to the G-quadruplex structure through intercalating into the cavity formed in the two G-tetrad planes and brings the tagging fluorophores closer together, thus resulting in FRET.

FRET is the radiationless transfer of energy from an excited donor fluorophore to a suitable acceptor fluorophore—a physical process that depends on spectral overlap and proper dipole alignment of the two fluorophores [78, 79]. With reduction in the donor fluorescence intensity and increase in the acceptor emission intensity, FRET occurs only when the donor fluorophore is excited by incident light and the acceptor is in its proximity. Its efficiency depends on the inter-fluorophore distance and spectral properties of donor and acceptor, as the donor fluorophore nonradiatively transfers its excitation energy to the acceptor fluorophore.

In earlier reports, two PSOs (PSO-1 and PSO-2) were applied for potassium detection. PSO-1 and PSO-2 are oligonucleotides which have human $[G_3(TTAG_3)_3]$ and *Oxytricha* $[G_4(T_4G_4)_3]$ telomere sequences carrying two fluorophores, FAM and TAMRA, at the 5′- and the 3′-end, respectively [74, 77]. In the unfolded structure of PSO, little FRET is expected since the average distance between the donor (FAM) and the acceptor (TAMRA) exceeds the critical radius. Under cation conditions, PSO-1 and PSO-2 were expected to form intramolecular quadruplex structures bringing the two tagging fluorophores close to each other, resulting in FRET (Fig. 3a). As the formation and stability of the quadruplexes is

cation dependent, the influence of metal cations, such as Mg^{2+} and Ca^{2+}, on the PSO probes was evaluated by FRET experiments. According to the report, interference of Mg^{2+} and Ca^{2+} was eliminated because they could not produce or cause only a slightly sensitized emission of TAMRA acceptor as a formation of parallel tetraplex resulting in fluorescence quenching [80, 81]. Although Na^+ has a larger FRET intensity than that of K^+ due to the specific spectral factor and steric interactions with the quadruplex structure, PSO-1 and PSO-2 are reported to have high selectivity for K^+ against Na^+, 43,000- and 150-fold, respectively [74]. Their differing selectivity might be relevant with their topologies: the former forms a basket-type quadruplex structure with three G-tetrads stabilized by two potassium ions and three loops consisting of three bases which do not participate in the formation of G-tetrad; the latter forms a basket-type quadruplex structure with four G-tetrads stabilized by three potassium ions and three loops consisting of four bases which do not participate in the formation of G-tetrad [23, 80]. Moreover, the overall selectivity is also affected by the FRET efficiency, with PSO-2 being smaller than that of PSO-1, presumably because the approach of the two fluorescent chromophores is hindered by the loop region with four bases instead of three in PSO-1.

Although PSO-1 and PSO-2 have been in principle available for the detection of potassium in the presence of sodium ions due to their relatively high selectivity, especially the former with a 43,000-fold selectivity, they cannot be applied for real-time K^+ monitoring under physiological conditions for the following reasons. i) The binding constant of the PSO/K^+ complex is too high, causing saturation of the probe at submillimolar K^+ concentrations. As in living organisms [K^+] is of molar level, PSO-1 and PSO-2 might provide relatively lower concentration of K^+ compared with its actual value. ii) FRET for PSO was more efficient with Na^+ than that of PSO/K^+ attributed to the distance between the fluorophores: in the presence of Na^+, PSO-1 and PSO-2 seem to form an intermolecular antiparallel structure with the fluorophores located side by side, while in the presence of K^+ they seem to form an intermolecular antiparallel structure with the fluorophores located in the diagonal corners, which is further than the former side by side pattern. Furthermore, Na^+ has been reported to be relevant with the higher quantum yield of donor emission, which may also be responsible for this phenomenon.

Recently, another probe, designated PSO-py, which exploits pyrene excimer emission for the transduction of the cation binding, has been reported [75]. In this method, TBA is applied to achieve the optimal potassium preference because it forms a chair-type quadruplex structure incorporating K^+ with a stoichiometry of 1 : 1. In the absence of K^+, PSO-py showed a random coil structure and gave only monomer emission. After adding K^+, both of the TBA termini were organized in a way that two tagging pyrene molecules were arranged face-to-face, producing efficient excimer emission without unwanted quenching phenomena of FAM and TAMRA. The interference of other metal cations was eliminated by their weak binding affinities, and the emission intensities of excimer fluorescence showed no positive responses to their concentrations. Compared with PSO-1 and PSO-2, PSO-py is highly recommended for real-time K^+ monitoring due to its advantages: i) it binds K^+ with a dissociation constant of 7.33 mM, which well matches the expected concentration range for K^+ and maximizes sensitivity; ii) it is likely to eliminate the interference of other

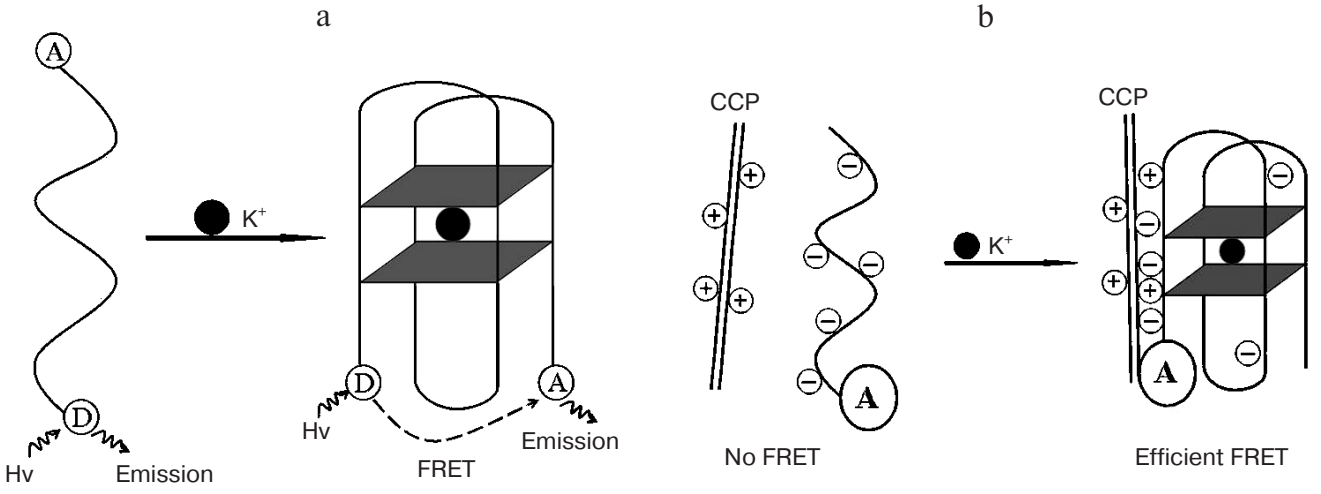


Fig. 3. Schematic illustrations of FRET. a) The donor (D) emits photons without acceptor (A) in proximity. In the presence of potassium ions, an antiparallel intramolecular quadruplex is formed bringing the two fluorophores closer. Then the acceptor takes the energy from the donor and emits photons. b) In the absence of potassium ions, TBA forms a random coil structure and no FRET is produced. Upon adding potassium, the stronger electrostatic interactions of G-quadruplexes with CCP lead to efficient FRET.

cations, especially Na^+ (37-fold, K_d = 272 mM); iii) it has reasonable sensitivity (ΔF of 8.3% per 1 mM K^+). Although it was reported to be the highest sensitive probe for potassium detection, the short excitation wavelength of pyrene is a drawback for its further application in potassium detection [82]. To circumvent this drawback, a dual-labeled oligonucleotide derivative, FAT-0, with FAM and TAMRA labels at the 5′ and 3′ termini of the TBA sequence, and its derivatives, FAT-*n* (*n* = 3, 5, 7, where *n* stands for the length of an additional sequence attached to the 5′ end of TBA sequence), were developed. All these probes were expected to provide relatively higher sensitivity by eliminating the dye–dye interactions between the fluorophores. In FAT-0, an apparent quenching of TAMRA emission was found due to the short distance (only the length of TBA). Then, FAT-*n* derivatives were applied by adding oligonucleotides at the 5′ end of the TBA sequence, increasing the distance relative to FAT-0, to eliminate unwanted quenching of TAMRA emission. The sensitivity of these probes for K^+ detection was measured by fluorescence measurements, which estimated the spacer effect between the donor and the acceptor on FRET efficiencies. Two probes, FAT-5 and FAT-7, showed improved performance for elimination of unwanted dye–dye interactions and could be applicable for K^+ detection. However, the major disadvantage of these probes is that their significantly lower binding affinity for K^+ should deteriorate the sensitivity the probes.

In 2005, He et al. reported another promising FRET-based technique combining the G-quadruplex structure of TBA and the amplification of FRET signal offered by cationic conjugated polymer (CCP) [76]. The main mechanism operates by taking advantage of the stronger electrostatic interactions of G-quadruplexes with CCP upon adding potassium ions. Its selectivity has been measured by the space charge density around the quadruplex that controlled the FRET signal transfer from CCP to fluorescein (Fig. 3b). According to the report, the FRET ratio (I_{527}/I_{422}) for K^+ is approximately 16 times higher than those for Na^+, and 6 times higher than those for Ca^{2+} and Mg^{2+}. To test the sensitivity of the probe, the FRET ratio of the probe was examined at different concentrations of Na^+ and K^+ in pure water. The probe can still detect 20 mM K^+ in the presence of 200 mM Na^+ with a 2.5 times higher selectivity. In this method, all the experiments were conducted in pure water without modulating pH and seemed too straightforward and neglected the sensitivity of the protolytic equilibria of fluorescein to the variation in ionic strength. However, it promises a potential probe applying G-rich single-stranded DNA and cationic conjugated polymers. With these facts, we are sure that a sensitive probe for K^+ detection is on its way by modulating the binding affinity and the characteristics of fluorophores and quadruplexes forming at various K^+ concentrations.

G-Quadruplex has been further investigated because it has been considered as a target for anticancer therapy and a probe for potassium detection. Most drugs have been reported to interact with the G-tetrad plane with the side chains intercalating with the quadruplex grooves and cause the disassociation of telomere proteins. Their anticancer function was the consequence of telomerase inhibition, hTERT alternative splicing, and the initiator of dysfunction of cell signal pathway. The polymorphism of quadruplex grooves promises possibilities for anticancer drug design to some extent, but great stringency is needed for specific quadruplex groove-interacting drugs. Based on the potassium sensing oligonucleotide and FRET, several probes for potassium detection have been developed. Their high selectivity and sensitivity enables the detection of potassium under physiological conditions – avoiding the interference of high levels of sodium ions – and promises to make real-time monitoring of potassium concentration possible in the future.

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