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On the feasibility of recognition of nucleic acid sequences by metal-ion-carrying oligonucleotides

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ABSTRACT

Metal-ion-mediated base pairing has been extensively studied in the context of DNA nanotechnology or expansion of the genetic alphabet but only recently with the aim of recognition of natural nucleic acid sequences. This review article focuses on the attempts to utilize metal-ion-carrying oligonucleotides as high-affinity probes for nucleic acids but relevant studies carried out at the monomer level are also discussed. Special emphasis is given to challenges inherent to this approach, such as the limited recognition elements of the canonical nucleobases and the scarcity of suitable metal ions in the intracellular medium. Finally, potential ways to overcome these challenges are proposed.

1. Introduction

Nucleic acids are an attractive but so far underexploited target in chemotherapy and diagnostics. Hybridization with a complementary oligonucleotide through Watson–Crick base pairing provides an elegant approach to recognize and potentially inhibit a given nucleic acid sequence with arbitrary selectivity. Yet most therapeutic agents that bind to nucleic acids, such as aminoglycoside antibiotics [1,2] or platinum-based anticancer drugs [3–5], rely on much less specific interactions. In the case of mRNA, however, the work of nearly three decades is finally coming to fruition with an increasing number of antisense oligonucleotides entering clinical trials [6].

In the last decade, small non-coding RNA molecules have emerged as a promising new target. For example, the miRNA profiles of many types of cancer are more characteristic than the respective mRNA profiles [7,8]. The utility of miRNA markers in cancer diagnostics is further increased by their remarkable persistence in the bloodstream [9]. The limited number of unpaired nucleobases, however, makes the recognition of miRNA sequences challenging compared to the relatively long single-stranded regions of mRNA. Modified oligonucleotide probes with enhanced hybridization properties would offer a solution to this problem [10].

Formal replacement of one or more of the hydrogen bonds of a Watson–Crick base pair by coordinate covalent bonds gives rise to a metal-ion-mediated base pair (Fig. 1) [11–17]. Owing to the much higher bond energy of the coordinate covalent bond, [18–20] such base pairs can be highly stabilizing. Until recently, the research on metal-ion-mediated base-pairing has focused on DNA nanotechnology, sensors for metal ions and expanding the genetic alphabet [21–25]. For such applications, both of the nucleobases of the metal-ion-mediated base pair may be designed for high affinity to the bridging metal ion as well as for compatibility with the steric requirements of the double-helix. Recognition of biologically relevant nucleic acid sequences, in turn, involves metal ion coordination by at least one natural nucleobase. In the case of therapeutic applications, the low intracellular abundance of suitable bridging metal ions presents an additional challenge.

2. Distinctive features between the canonical nucleobases

The predominant coordination sites for metal ions are N3 of pyrimidine and N1 and N7 of purine bases [26]. The former two are part of the Watson–Crick face and, hence, well positioned for coordinating a bridging metal ion in an antiparallel double helix (Fig. 2A and B). The latter may, upon rotation of the purine base about the N-glycosidic bond, also engage in metal-ion-mediated base pairing, giving rise to a Hoogsteen type pair (Fig. 2C). Discrimination between the canonical nucleobases may be based on properties of the donor atom itself or the substitution pattern around it.

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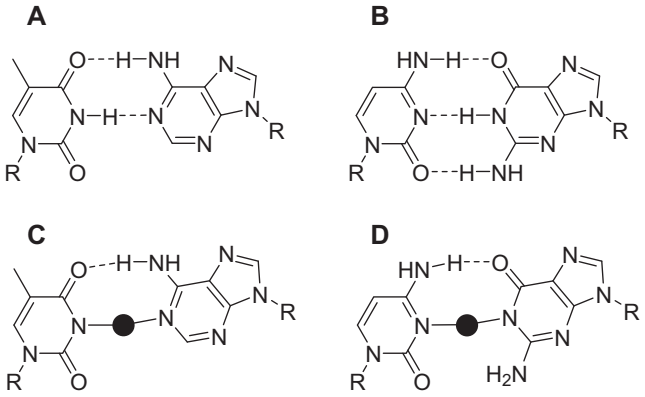

Fig. 1. Watson–Crick base pairs T:A and C:G (A and B, respectively) and their metal-ion-mediated counterparts (C and D, respectively). Due to the longer N3–N1 distance in the latter, only one of the interligand hydrogen bonds is retained [10].

2.1. Basicity of the donor atom

Barring steric hindrance, the affinity of an endocyclic nitrogen atom of a nucleobase for a given metal ion is dictated by the basicity of the nitrogen atom. The pK_a values of the primary donor atoms of the canonical nucleosides are 9.6, 9.3, 4.3 and 3.6 for guanosine-N1, uridine-N3, cytidine-N3 and adenosine-N1, respectively [27]. The most basic donor atoms are, hence, protonated under physiological conditions but metal ion coordination may compete with protonation. The pH where metal ion coordination takes over depends on the metal ion in question, as well as the steric bulk of its other ligands. For example, with the metal ions most often employed in metal-ion-mediated base pairing, the crossover pH for guanosine N1 ranges from 5.6 (for $CH_3Hg(II)$) to 7.8 (for Ni(II)) [27]. Deprotonated guanosine and uridine coordinate metal ions much more strongly than neutral adenosine and cytosine and this difference may be exploited for nucleobase recognition. For example, at the monomer level the Pd(II) chelate of 2,6-bis(3,5-dimethylpyrazol-1-yl)purine riboside favored with guanosine- and uridine-5′-monophosphates over the respective adenosine and cytidine nucleotides and this selectivity was also reflected in the hybridization of respective Cu(II)-chelating oligonucleotides [28,29]. Discrimination between guanine and uracil based solely on the basicity of their donor atoms, however, may prove exceedingly challenging.

2.2. Hydrogen bond acceptors and donors

Stabilization of the desired metal-ion-mediated base pair by additional hydrogen bonding interactions would result in selectivity beyond what is achievable through metal coordination alone. Base pairing mediated by one Ag(I) ion and one hydrogen bond has been demonstrated between thymine and both 1-deaza- and 1,3-dideazaadenine but the selectivity of thymine recognition was not investigated in detail [30,31]. The C:C mispair is selectively stabilized by Ag(I) and quantum chemical calculations predict the *trans* conformation, enabling interligand hydrogen bonding, to be favored by this Ag(I)-mediated base pair [32–34]. A recent crystal structure of an RNA duplex incorporating two C–Ag(I)–C base pairs, on the other hand, clearly shows this oligonucleotide to adopt the canonical A-form secondary structure, with the C–Ag(I)–C pairs in *cis* conformation [35]. Indeed, transoid base pairs are typically found only in parallel-stranded duplexes. The importance of the interligand hydrogen bond in formation of a C–Ag(I)–C base pair remains, hence, questionable.

2.3. Steric blockers

Besides stabilizing the desired metal-ion-mediated base pair through hydrogen bonding, discrimination between nucleobases may also be achieved by destabilizing mispairs through steric repulsion. An amino substituent is sterically more demanding than an oxo substituent which, in turn, is more demanding than a hydrogen atom. Among the canonical nucleobases, adenine is the only one where the primary donor atom of the Watson–Crick face (the N1) is flanked by only one substituent and could potentially be recognized by sterically demanding metal chelates. A number of metal chelates indeed prefer binding to adenine over the other canonical nucleobases [29,36,37] but the data available do not allow unambiguous correlation of this preference with the steric bulk of the chelate. At the monomer level, Pd(II) chelates of *N*-alkylated dipicolinamides favor coordination to the more accessible N7 site of guanosine-5′-monophosphate whereas the unsubstituted parent chelate favors coordination to N1 [38]. To what extent these results apply at the oligonucleotide level remains to be investigated.

3. Coordination geometry

The requirement for planarity of base pairs within the base stack of a double helix limits the number of coordination geometries amenable to metal-ion-mediated base pairing. So far, base pairs featuring linear, trigonal planar (or trigonal bipyramidal) and square planar (or octahedral) geometry around the bridging metal ion have been incorporated into oligonucleotide duplexes. In addition, pentagonal bipyramidal coordination appears an as yet unexploited possibility.

Even if the metal ion and the donor atoms around it lie in a plane, rotation about the coordinate bonds may result in deviation of the metal-ion-mediated base pair from the desired coplanar conformation (Scheme 1A). Such rotation typically takes place to alleviate steric clash between the two ligands, presenting a major challenge when studying the selectivity of metal-ion-mediated base pairing at the monomer level [28,38,39]. A thoroughly studied example are the Pd(II) and Pt(II) chelates of terpyridine that accept most aromatic ligands at the vacant coordination site of the metal ion only in a nearly perpendicular orientation [40]. Only N3-coordinated tetrazoles, with no substituents (even hydrogen atoms) vicinal to the donor atom, readily adopt a nearly coplanar orientation relative to terpyridine. Multidentate coordination of both

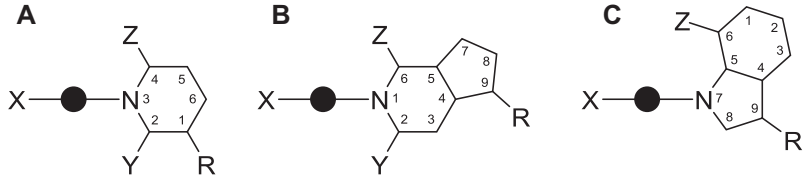

Fig. 2. Metal-ion-mediated base pairing between an artificial ligand (X) and N3 of pyrimidines (A) and N1 (B) or N7 (C) of purines. The potential recognition elements of the canonical nucleobases have been indicated as Z and Y.