Review

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DNA-bound metal ions: recent developments

Abstract: The affinity of metal ions for DNA is logical considering that the structure of DNA includes a phosphate backbone with a net-negative charge, a deoxyribose sugar with O atoms, and purine and pyrimidine bases that contain O and N atoms. DNA-metal ion interactions encompass a large area of research that ranges from the most fundamental characterization of DNA-metal ion binding to the role of DNA-bound metal ions in disease and human health. Alternative DNA base pairing mediated by metal binding is also being investigated and manipulated for applications in logic gates, molecular machines, and nanotechnology. This review highlights recent work aimed at understanding interactions of redox-active metal ions with DNA that provides a better understanding of the mechanisms by which various types of oxidative DNA damage (strand breakage and base modifications) occur. Antioxidants that mitigate oxidative DNA damage by coordinating metal ions that produce reactive oxygen species are addressed, as well as recent work on the effect of DNA-metal ion interactions and the efficacy of quinolone-based antibacterial drugs. Recent advances in metal-mediated base pairing that triggers conformational changes in DNA structure for use as selective metal ion sensors and novel nanotechnology applications are also included.

Keywords: antioxidants; DNA; metal ion binding; metal-mediated base pairing; oxidative DNA damage.

DOI 10.1515/bmc-2014-0021
Received July 10, 2014; accepted August 14, 2014

Introduction

Metal ions are essential to numerous biomolecular processes. Mg^{2+} and Zn^{2+} are common examples that function as cofactors in enzymatic reactions. The structure of DNA, with its phosphate backbone, deoxyribose sugar with O atoms, and bases containing N and O atoms, makes it a natural target for metal ion binding. The ultimate effects and long-range consequences of DNA-metal interactions depend on many different factors, including the identity of the metal ion, its speciation, redox activity, and the actual site(s) of binding on the DNA macromolecule. Normal pairing between bases of separate DNA strands comprises the secondary structure of DNA and arises from hydrogen bonding between adenine (A) and thymine (T) bases, and between guanine (G) and cytosine (C) bases. This base pairing produces the tertiary double-helical structure of double-stranded DNA that creates a small gap 'minor groove' that is AT rich and a larger 'major groove' that is GC rich. These grooves allow metal ions, small molecules, and complex ions to interact with DNA bases directly. The structure of DNA and the various modes of metal ion binding to the phosphate backbone, deoxyribose sugar, and specific nucleobases have been reviewed (1–3). Metal ion binding to the phosphate backbone (e.g., Mg^{2+} ions) tends to stabilize the DNA double helix because this neutralizes the excess negative charge from the phosphate groups. Outer-sphere complexes with metal ions are formed when a fully hydrated metal ion is coordinated with a ligand indirectly through water molecules, whereas inner-sphere coordination complexes are stronger interactions in which coordinated water molecules with the metal ion and/or ligand are displaced, allowing the ligand to coordinate directly with the metal ion. Transition metal ions tend to produce inner-sphere complexes with DNA bases. It is generally accepted that metal ions bind to the purine bases G and A through the N7 atom. The O6 atom of G and the N1 atom of A are also metal ion binding sites. The pyrimidine bases T and C bind metal ions through the O2 and N3 atoms, respectively. Figure 1 shows the structures of the four DNA bases. The N and O atoms that participate in metal ion binding are numbered.

Bound metal ions influence the nature and stability of the secondary and tertiary structures of DNA, and DNA is subject to modifications from subsequent reactions of these metal ions with other species. The importance of DNA-metal interactions and their relevance to disease and medicine is a vast area, and they have the potential of

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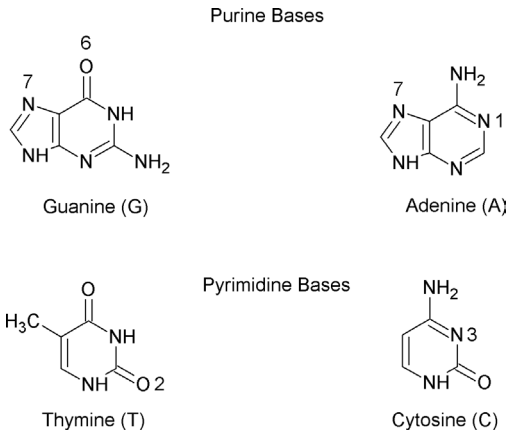

Figure 1 Structures of the purine bases guanine (G) and adenine (A) and the pyrimidine bases thymine (T) and cytosine (C).
The N and O atoms that generally coordinate with metal ions are numbered.

being harnessed for applications in several areas, including metal-dependent DNAzymes for catalytic cleavage of DNA substrates and DNA-based sensors for metal ions (4–7). This review focuses on recent advances in understanding fundamental aspects of metal-DNA interactions, their relation to metal-mediated oxidative DNA damage, and antioxidants that function by binding metal ions. Drugs that are influenced by DNA-bound metal ions and some recent developments in metal-dependent alternative DNA base pairing are also addressed.

Metal-mediated oxidative DNA damage

Metal ions (such as K^+, Na^+, and Mg^{2+}) are essential to DNA stability as they neutralize the net negative charge arising from the phosphate backbone (3). Many DNA-metal ion interactions are sequence specific and play vital roles in the correct functioning of DNA-related enzymes (e.g., the frequent role of Mg^{2+} as an enzyme cofactor). However, these interactions can have adverse effects under certain conditions. The cytotoxic effects of many metals arise from metal ion binding to DNA bases. A prime example is Hg(II) ion and Hg(II) compounds, which disrupt the hydrogen bonds between naturally occurring A-T base pairs and form T-Hg^{2+}-T pairs (8, 9). Redox-active metal ions are receiving much attention because of their ubiquitous presence in biological systems and their abilities to react with H_2O_2 and other endogenous oxidizing agents to produce damaging reactive oxygen species (ROS), and an important topic in metal toxicity and carcinogenesis is metal-mediated oxidative DNA damage (10–13). One of the most common examples is Fe(II). Fe(II) in the presence of H_2O_2, a product of aerobic metabolism, can react to produce hydroxyl radical (·OH) through the Fenton reaction (14):

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + {}^{\cdot}OH.$$

Different metal ions give rise to different types and degrees of oxidative DNA damage, and metal ions that produce ROS through Fenton-like reactions with H_2O_2 include Fe(II), Cu(II), Cr(III), Cr(VI), V(III), Co(II), Ni(II), Cd(II), and Zn (15). In the presence of reductants (e.g., ascorbate), Cu(II) is reduced to Cu(I), which can react with H_2O_2 in a Fenton-like manner to produce Cu(II), OH^-, and ·OH:

$$Cu^+ + H_2O_2 \rightarrow Cu^{2+} + OH^- + {}^{\cdot}OH.$$

However, even when reductants are not added, Cu(II) still reacts with H_2O_2 to produce ROS that behave very similarly to ·OH (15–18). The suggested mechanism of oxidative DNA damage arising from Cu(II) involves a process in which Cu(II) is bound to a G-containing moiety in DNA and reduced to Cu(I) (16, 19–21). The ROS produced from this mechanism are suggested to be Cu(I)-peroxide complexes, with reactivity similar to that of ·OH, or singlet oxygen ($^1O_2$) as opposed to hydroxyl radical (·OH) (19–21).

Base modifications

The ability of DNA to bind metal ions that are capable of producing ROS makes DNA-bound metal ions an important aspect of understanding the mechanism of ROS generation and the correlation of site-specific oxidative DNA damage to diseases and disorders (13, 22–25). Oxidative DNA damage from ROS ranges from single- and double-strand breaks to modified DNA bases. Nucleobase modifications can lead subsequently to DNA strand scission (26), and these various forms of DNA damage are associated with numerous diseases and conditions, including kidney disease and diabetes (27), certain types of cancer (12, 28), hypertension (29), and aging (30, 31). In some cases, however, this damage is desirable, especially in chemopreventive and chemotherapeutic applications if it can be targeted and controlled to prevent DNA from replicating in tumors (32–35). G is the most easily oxidized DNA base, and it exhibits the largest degree of damage, producing several G-based derivatives including the accepted oxidative DNA damage marker

8-hydroxy-2′-deoxyguanosine (8-OH-dG) (17, 36–38). The structures of the mononucleoside 2′-deoxyguanosine (dG) and the accepted oxidative damage marker 8-OH-dG and its keto form 8-oxo-2′-deoxyguanosine (8-oxo-dG) are presented in Figure 2. The transition metal ions Fe(II), Cu(II), Cr(III), and V(III) produce significant levels of 8-OH-dG in the presence of H_2O_2 (15), and the Cu(I)/H_2O_2 system also yields significant 8-OH-dG levels (17). The reactive nature of radical species suggests that they are generated close to the site at which they react. In general, single-strand breaks are a form of generalized damage associated with ROS generated free in solution, and double-strand breaks are closely correlated with 8-OH-dG levels, suggesting that they arise from ROS generated in close proximity to the G base (15, 18, 39). Figure 3 illustrates ROS production and the resulting types of damage from metal ions free in solution and those bound to the phosphate backbone and/or individual bases of DNA. Characterizing the interactions between metal ions and the nucleobases and phosphate groups of DNA, and correlating them with products that result from oxidative DNA damage is ongoing. Nitrogen-15 nuclear magnetic resonance (NMR) spectrometry provides insight into the formation of coordination and covalent bonds between metal ions and N atoms on nucleobases (40), and this type of site-specific metal coordination is expected to correlate closely with formation of very specific DNA base modifications (e.g., 8-OH-dG production).

Metal-mediated oxidation of DNA and the G base in particular is complicated. The products that result from the mononucleoside dG and single- and double-stranded oligodeoxynucleotides when ROS are produced form the Cu(II)/H_2O_2 system in the presence of the reductants ascorbate and *N*-acetylcysteine were characterized recently by Fleming et al. They observed a total of 10 different dG oxidation products, including the G base itself. They proposed mechanisms that account for their observation that the major oxidation product in this study was 5-carboxamido-5-formamido-2-iminohydantoin (d2lh), which results from an overall two-electron oxidation of

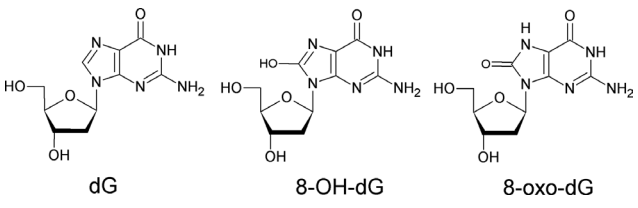

Figure 2 Structures of the mononucleoside 2′-deoxyguanosine (dG), the site-specific oxidative damage marker 8-hydroxy-2′-deoxyguanosine (8-OH-dG), and its keto form 8-oxo-2′-deoxyguanosine (8-oxo-dG).

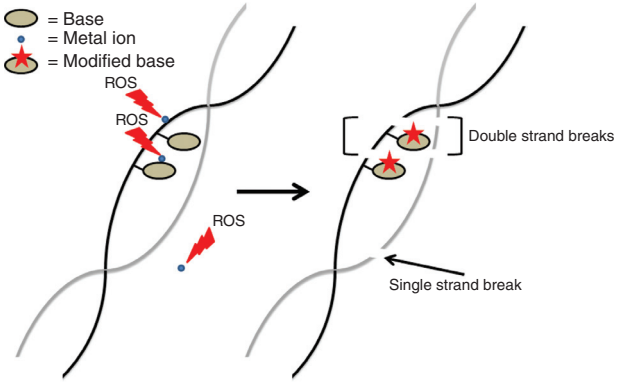

Figure 3 Illustration of ROS formation and oxidative DNA damage from metal ions free in solution and metal ions bound to the phosphate backbone and individual bases.
The strong correlation between site-specific modification of bases (e.g., 8-OH-dG) and double-strand breaks suggests that both types of damage result from ROS generated by DNA-bound metal ions. Single-strand breaks are indicative of less site-specific ROS production (e.g., from metal ions free in solution).

dG at the C5 position. Oxidation at the C8 position leads to the accepted oxidative damage marker 8-oxo-dG (the keto form of 8-OH-dG). Coordination of Cu at the N7 position of dG appears to play a major role in both C5 and C8 oxidation. A Cu(III)-OH species at the N7 position is suggested to yield a 5-OH-dG intermediate in C5 oxidation (which leads to the major product d2lh) and the 8-OH-dG tautomer in C8 oxidation. The product distribution also contained species that arise from oxidation of the deoxyribose sugar with the identity of the reductant affecting whether oxidation took place at the C5 or C8 carbons of dG or at the deoxyribose sugar (41).

Iron, copper, and chromium reactions

The metal ions Fe(II), Cu(I), Cu(II), and Cr(III) are often studied because of their abilities to produce significant levels of the site-specific 8-OH-dG oxidative DNA damage marker, and iron and copper are also interesting because they are endogenous to living systems and exhibit dual behaviors as essential elements and cytotoxic agents depending on concentration. Extended X-ray absorption fine structure spectroscopy of a solid Fe(II)-DNA complex indicates that the inner coordination sphere of Fe(II) contains five O atoms and one N atom, confirming that Fe(II) interacts with nucleobases through N atoms. Values of the Fe-O and Fe-N distances in the inner coordination sphere were also reported (1.99±0.02 and 2.22±0.02 Å, respectively) (42). Most studies indicate that Cu(II) interacts with

DNA primarily through N7 of the G base (43–46). Cu(II) has been reported to exhibit preferential binding at polyguanosine sequences with at least two adjacent G bases (16), and DNA-fiber electron paramagnetic resonance (EPR) spectroscopy has demonstrated that aqueous Cu(II) can bind to DNA in both a mobile mode and a mode in which the orientation of the coordination plane is fixed (47). Cr(III) is generally believed to bind to DNA through the G base and an adjacent phosphate group (43, 48).

Noblitt et al. employed the mononucleoside dG and the mononucleotide 2′-deoxyguanosine-5′-monophosphate (dGmp) as simple models to differentiate the interactions of the metal ions Fe(II), Cu(II), and Cr(III) with the dG base and/or the phosphate group that lead to the production of 8-OH-dG. Not surprisingly, the different metal ions produced different levels of 8-OH-dG depending on whether they interacted with the base only (the mononucleoside dG) or the base and/or the phosphate group (dGmp). The level of 8-OH-dG production from Fe(II)/H_2O_2 was substantially larger for the mononucleotide (dGmp) than the mononucleoside (dG), suggesting a combined interaction of Fe(II) with N7 of the G base and the adjacent phosphate on the mononucleotide. No difference in the yields of 8-OH-dG from dG and dGmp was observed for Cu(II)/H_2O_2; however, the Cr(III)/H_2O_2 system produced higher levels of 8-OH-dG formation from dG. It was concluded that Cu(II)-N7 and Cr(III)-N7 interactions with the G base favor the production of 8-OH-dG (49).

DNA-bound Cu(II) is reported to be responsible for enhancing 8-OH-dG formation in the presence of the sugars glucose and fructose. While glucose and fructose alone were shown to increase 8-OH-dG levels, a dramatic increase was observed when Cu(II) was present. The fructose/Cu(II) system generated significantly more 8-OH-dG damage marker than the glucose/Cu(II) system. The enhanced ability of the fructose/Cu(II) system to cause oxidative damage is suggested to proceed by a mechanism where fructose (a reducing sugar) reduces DNA-bound Cu(II) to produce a ·fructose (enediol radical anion)-DNA-Cu^+ complex. This complex can react subsequently with H_2O_2 to produce a DNA-Cu^+-OOH complex, regenerating fructose (50). This study is significant because it connects DNA-bound Cu(II) with many of the observations associated with diabetes, including elevated fructose levels, release of metal ions from intracellular stores [including Cu(II)], and elevated levels of 8-OH-dG.

Recent interest in Cu(II)-DNA interactions is associated with its role in neurodegenerative diseases, and Ando et al. demonstrated the connection of Cu(II)-DNA binding and the neurotransmitter dopamine in conformational DNA changes and oxidative DNA damage. It is reported that Cu(II) is preferentially bound to adjacent G bases, and dopamine reduces Cu(II) to Cu(I), followed by a conformational change in DNA to accommodate a coordination geometry rearrangement. The oxidative DNA damage marker 8-oxo-dG was produced when H_2O_2 was introduced, supporting a Fenton-type reaction between Cu(I) and H_2O_2 that produces ·OH (51).

Solivio et al. report the formation of a lysine derivative of G when the mononucleoside dG is combined with an acylated lysine derivative in the presence of the Cu(II)/H_2O_2/ascorbate system. The proposed mechanism for forming the lysine-G adduct from dG begins with the formation of 8-oxo-dG from ·OH produced from the reaction between Cu(I) and H_2O_2. The same lysine-G derivative was also observed in reactions employing a 14-nucleotide duplex (oligonucleotide) and a larger 392-nucleotide DNA substrate. The reactions involving the larger DNA substrate demonstrate that adducts form predominately at polyguanosine residues (specifically at a 5′-GGG position), and this study shows that the presence of Cu (free or bound to DNA or proteins) can induce DNA-protein cross-link formation and other DNA modifications that can occur under oxidative conditions (52).

Interactions between different metal ions also affect the degree and type of oxidative DNA damage (8-OH-dG formation and strand breaks) from Fenton or Fenton-like reactions. Moriwaki et al. studied the abilities of Fe(II), Cd(II), Ni(II), Cr(III), Cu(II), and binary mixtures thereof to produce 8-OH-dG and DNA strand breaks through Fenton-type reactions. Notably, Fe(II) and Cu(II) exhibited fewer strand breaks and lower quantities of 8-OH-dG when combined with Ni(II). Mixtures of Fe(II) and Cr(III) produced an additive effect on 8-OH-dG formation, whereas Cu(II) and Cr(III) together increased 8-OH-dG production in a synergistic manner. Interestingly, the degree of strand breakage for the Fe(II)/Cr(III) and Cu(II)/Cr(III) systems did not reflect the increases in 8-OH-dG yields. In most cases, double-strand breaks were not observed with the exceptions being the Fe(II)/Cr(III) and Fe(II)/Cu(II) mixtures (53). These results reflect the various DNA binding sites preferred by different metals, and confirm that DNA strand breaks and 8-OH-dG formation, although related, arise from different mechanisms.

Antioxidants that coordinate metal ions

Many antioxidants function as ROS scavengers by reacting sacrificially with ROS before surrounding structures

are damaged. However, studies of antioxidants in the realm of metal-mediated oxidative DNA damage suggest that metal ion coordination is a critical part in the mechanism of some antioxidants. Several sulfur (S) and selenium (Se) compounds function as antioxidants through a mechanism that involves coordinating the metal ions that produce ROS (54). However, metal ion coordination is only one step in the mechanism, and many questions remain. Recent work has attempted to address these questions.

Selenium compounds

The organoselenium compounds selenocysteine and selenomethionine function as antioxidants in reactions involving Cu(I) through coordinating the Cu ions (55, 56). Methyl-selenocysteine exhibited the ability to minimize oxidative DNA damage by coordinating both Cu(I) and Fe(II), and whereas selenocystamine exhibited antioxidant activity for reactions involving both Cu(I) and Fe(II), there was evidence that it formed a coordination complex only with Fe(II) (56). The inorganic Se compounds Se dioxide (SeO_2) and sodium selenite [Na_2SeO_3, which dissociates in aqueous solution to produce the selenite ion (SeO_3^{2-})], also appear to function as antioxidants in reactions involving Fe(II), Cu(II), and Cr(III) by coordinating these metal ions (57, 58). All of these compounds exhibit different levels of protection, and the extent of antioxidant behavior also depends on the identity of the metal ion. Hart et al. investigated the abilities of SeO_2 and SeO_3^{2-} to coordinate these metal ions before and after they had the opportunity to bind to DNA by monitoring levels of the site-specific oxidative DNA damage marker 8-OH-dG (58). SeO_2 and SeO_3^{2-} lowered 8-OH-dG levels for reactions involving Fe(II) and Cu(II) even when the metal ions were first combined with DNA, and their effectiveness as antioxidants increased significantly for the Fe(II) and Cr(III) reactions when these metal ions were preincubated with the Se compounds before adding DNA. These results indicate that SeO_2 and SeO_3^{2-} are capable of coordinating DNA-bound Fe(II) and Cu(II) and lowering oxidative damage to a limited extent. However, it is not clear from this study if the Se compounds extract bound metal ions from DNA to produce complexes free in solution or if DNA-metal-Se coordination complexes form. In addition, questions still remain concerning whether the Se-metal complexes are unreactive toward H_2O_2 (due to a shift in the redox potential of the complexed metal ion), if ROS are formed and scavenged by the Se compound, or if ROS are produced but lead to more generalized DNA damage (e.g., single-strand breaks) rather than the site-specific marker 8-OH-dG.

Sulfur compounds

The antioxidant activity of S-containing compounds in metal-mediated oxidative DNA damage studies also correlates with their abilities to bind metal ions. Cystine, cysteine, methyl-cysteine, and methionine are all reported to form coordination complexes with Cu(I) and lower oxidative DNA damage. The reduced and oxidized forms of glutathione also lowered Cu(I)-induced oxidative DNA damage through a mechanism that appears to involve Cu(I) binding. The S compound 3-carboxypropyl disulfide showed no antioxidant activity toward Cu(I)/H_2O_2 oxidative damage; however, it did lower Fe(II)-mediated damage through a mechanism that appears to involve metal coordination (59). The S compounds methionine sulfoxide and methylcysteine sulfoxide also exhibited antioxidant activity toward the Cu(I)/H_2O_2 system in a matter consistent with Cu coordination; however, in this case, it appears that metal coordination alone does not account for all of the antioxidant activity. Specifically, these results indicate that, in some cases, antioxidant activity may be a combination of metal ion coordination and ROS scavenging (60).

DNA-metal ion binding and drug interactions

Metal-DNA interactions are the basis of numerous anticancer drugs, antiviral drugs, and antibacterial agents. The majority of these species function by intercalating into the DNA structure, and this behavior can be manipulated by forming metal coordination complexes with the drug. Common metal centers for these drugs include Ru, Os, Co, Ni, Cu, and Zn. The discovery of the chemotherapeutic metal-based drug cisplatin is one of the prime examples of the manipulation of metal-DNA interactions in fighting diseases. Cisplatin (*cis*-[$PtCl_2(NH_3)_2$]) is a metal complex, and the basis of its effectiveness involves the ability of the Pt to coordinate with the N7 atom of the G base to form numerous adducts. Several workers have reviewed the area of metal complexes and DNA interactions (5, 61–63).

DNA-metal complex interactions

Delivery of chemotherapeutic agents as structured nanoparticles has the potential to employ the cytotoxic effects of bound metal ions and metal complexes in a targeted fashion. A heterobimetallic complex containing Cu(II)

and Sn(IV) coordinated with pyrazole and phenyl glycine chloride ligands was shown to interact with calf thymus DNA (CT-DNA) through an electrostatic interaction and induce condensation to a particulate nanostructure. The complex also exhibited oxidative cleavage activity toward plasmid DNA. Besides forming a condensed nanoparticulate form of DNA, which allows transportation across cell barriers and resistance to enzymatic degradation, a key and novel feature of this complex is reported to be its dual-binding mode to DNA that arises from Cu(II) binding to the N7 of the G base and Sn(IV) interacting with the phosphate backbone (64).

Complexes of Cu(II), Co(II), and Ni(II) of the form $[M(H_2O)_3(SO_4)(4\text{-CNpy})_2] \cdot H_2O$ (where 4-CNpy is 4-cyanopyradine) were found to exhibit the same solid and solution phase structures. Their solution phase structure was reported as $[M(H_2O)_4(4\text{-CNpy})_2]^{2+}$, which exhibited strong binding with CT-DNA. The binding stoichiometry was dependent on the identity of the metal ion, and a noteworthy feature of this study was that it employed isothermal titration calorimetry (ITC) to study the thermodynamics of the binding interaction (65). ITC has been employed to observe the thermodynamics of DNA binding with metal complexes (66–68), and its applicability to binding of metals and metal complexes with DNA is expected to increase (65). It is being employed in studying alternative base pairing mediated by metal ions, which is addressed in a later section.

Quinolone-based antibacterial agents

The mechanism by which quinolone-based antibacterial agents function is not fully understood; however, it is believed that they function as bacterial topoisomerase inhibitors by forming complexes with DNA and the bacterial enzymes topoisomerase II (DNA gyrase) or topoisomerase IV. This binding interaction ultimately leads to DNA cleavage and bacterial cell death. Quinolone antibacterial agents have been reviewed (69), and recent work supports the role of DNA-bound metal ions in the quinolone-DNA interaction. Quinolones are capable of binding to the phosphate groups of DNA through the carboxyl and carbonyl moieties, and it has been demonstrated that the presence of DNA-bound metal ions can enhance or inhibit this binding in a manner dependent on both the identity of the metal ion and its concentration. Mg^{2+} ions are reported to play a major role (cofactor) in the DNA cleavage-rejoining activity of topoisomerases (70), and the presence of Mg^{2+} was noted to have an effect on quinolone binding to DNA. Recent work has demonstrated that at low concentrations (<3.0 mM), Mg^{2+} ions enhance quinolone binding to DNA by binding to phosphate groups on the DNA and creating a bridge for the interaction of the quinolone with the phosphate groups (71, 72). Cu^{2+} also increases the binding interaction with several quinolones and DNA by interacting with the drug molecule and DNA bases. However, for the case of the quinolone sparfloxacin (SPFX), which also has an amino group with which it can bind directly to a DNA base, the presence of Cu^{2+} decreased the binding affinity because of a possible competitive binding interaction between Cu^{2+}, DNA bases, and SPFX (71). An interesting comparison of metal ions and their abilities to enhance quinolone-DNA binding is Cr(III) and Cr(VI). Cr(III) does not bind to SPFX as strongly as Cr(VI); however, increasing amounts of Cr(III) increase the SPFX-DNA binding constant. This is explained by the ability of Cr(III) to bind mainly to DNA bases at low concentrations and bind to phosphate groups at higher concentrations, thus increasing the SPFX-DNA binding constant. While Cr(VI) coordinates with SPFX, it does not have a high affinity for DNA, and the presence of Cr(VI) had no effect on the binding constant between SPFX and DNA (48). The binding interaction between SPFX and DNA decreases in the presence of Cd^{2+}, which is reported to bind mainly to DNA bases, indicating that Cd^{2+} competes with SPFX for DNA binding sites (72).

Alternative DNA base pairing using metal ion coordination

Base pairing through hydrogen bonding is essential to the correct form and function of DNA, and any disruptions in this relatively strong intermolecular force can lead to destabilization of the DNA double helix. However, researchers are starting to ask the question ‘What if hydrogen bonding was replaced with another attractive force for DNA base pairing?’ Not only would the DNA conformation be different but also other properties would change, including the conditions (temperature, ionic strength, and pH) at which DNA melts (i.e., the strands in double-stranded DNA separate to form single-stranded DNA). The double-helical structure of DNA could have other applications if these physical properties could be ‘tuned’ through the pattern and strength of base pairing. Metal ion-mediated base pairing (metallo-base pairing) is being studied as an alternative to hydrogen-bonded base pairing. In addition to forming base pairs between naturally occurring bases, metallo-base pairing using synthetic ligands

that behave like nucleobases allows base pairing that is orthogonal to naturally occurring base pairs, opening opportunities to expand genetic information and information storage capabilities. Metal-mediated base pairing involving naturally occurring bases and synthetic nucleobases is a rapidly expanding area for which several reviews exist (73–76).

Mismatched base pairs from naturally occurring nucleobases have been achieved using Hg(II) and Ag(I) ions. As early as 1963, a 2:1 T-Hg complex (T-Hg^{2+}-T) was theorized to exist in duplex oligonucleotides (8), and binding of Hg(II) and CH_3Hg(II) to N3 of T was shown to be thermodynamically favored over binding to N1 of G (77). The stabilizing effect of this interaction was demonstrated using UV melting, and the specificity of Hg(II) for the T-T mispairs was confirmed along with formation of a double-helical duplex structure consisting of only T-Hg^{2+}-T pairs. NMR studies demonstrated that Hg(II) displaces the imino proton on N3 of T to form the T-Hg^{2+}-T pairs (78, 79). Recent work involves characterizing further the T-Hg^{2+}-T interaction using ITC to obtain thermodynamic data. It is reported that double T-T mismatches can be paired with two stoichiometric quantities of Hg(II), and the binding affinity of the second Hg(II) ion is more favorable than the first, resulting in positively cooperative binding. It is suggested that this may be favorable for aligning multiple Hg(II) ions in duplex DNA for use in nanotecholoogy applications (80). Stable duplexes containing C-C pairs were reported in the presence of Ag(I), and it was concluded that Ag(I) binds selectively to the C-C mismatch. A DNA-based Ag(I) sensor was developed on the basis of this behavior (81). The thermodynamic properties of this very specific C-Ag^{+}-C pair were investigated using UV melting and other techniques including ITC. Only a duplex containing the C-C mismatch was stabilized in the presence of Ag(I), and 1:1 binding between Ag^{+} and the C-C pair was reported with a binding constant of 10^6 M^{-1} (76, 82). A noteworthy example of artificial base pairing that results in an exceptionally stable duplex was achieved by pairing salicylic aldehyde nucleobase derivatives incorporated into an oligonucleotide with the metal ions Cu(II) and Mn(II). In addition to base pairing, the duplex was further stabilized by adding ethelynediamine as an additional cross-linking agent (83).

Base pairing and conformational changes

The incorporation of a single metal-base pair into a DNA duplex shows a marked increase in duplex stability. Besides DNA duplexes, other structures, including hairpin loops and triple-stranded DNA, can be formed and manipulated by metal-mediated base pairing. Kuklenyik and Marzilli demonstrated that forming Hg(II)-mediated base pairs in oligonucleotide sequences containing different numbers of mismatched T residues influenced conformational changes between hairpin and duplex forms (84). Taking advantage of the absence or presence of metal ions to induce conformational changes between hairpin loops and duplexes in these structures has several applications as DNA-based metal ion sensors, devices, and machines. The T-Hg^{2+}-T base pair mentioned above was employed as an integral part of a fluorescence-based Hg(II) sensor in which base pairing results in a hairpin structure that increases fluorescence resonance energy transfer (FRET) between donor-acceptor groups attached to the ends of an oligonucleotide (85). Base pairing from the addition of Ag(I) was demonstrated for a 1,2,4-triazole nucleoside incorporated into an oligonucleotide sequence. The oligonucleotide existed in a hairpin structure when Ag(I) was absent, and addition of Ag(I) resulted in the formation of a regular double-helix conformation. This conformational change also holds promise as an Ag(I) sensor, as the conformational change from hairpin to double helix results in fluorescence quenching through FRET (86). Other examples of conformational changes based on metal-mediated base pairing include imidazole nucleotides that are paired upon adding Ag(I) ions and T-C-rich oligonucleotides that bind Hg(II) and Ag(I), promoting a conformational change from a random coil to a hairpin (87). Very recently, a set of nucleosides was developed on the basis of 1,2,3-triazole with 1,2,4-triazole, pyrazole, and pyridine complements, producing bidentate nucleosides that form base pairs in the presence of Ag(I). This set of synthetic nucleosides was aimed at understanding further the various effects that stabilize duplexes formed from metal-mediated base pairing (88).

Metal-mediated pairing of natural bases has also resulted in DNA-based logic gates. Applications include CdSe/ZnS quantum dots with nucleic acid functional groups that use Ag(I) and Hg(II) ions as inputs (89), and PCR amplification that proceeds only when Hg(II) and Ag are available to form T-Hg^{2+}-T and C-Ag^{+}-C base pairs (90). A unique development in DNA-based logic gates involves using gold nanoparticles (AuNPs) that have been modified with either T- or C-rich oligonucleotide strands. Addition of Ag(I) and Hg(II) (inputs) results in a conformational transition (due to the formation of C-Ag^{+}-C and T-Hg^{2+}-T base pairs) that leads to aggregation of the modified AuNPs and a distinct color change in the visible region of the electromagnetic spectrum. The aggregation can be

reversed by addition of EDTA and NH_4OH to capture Hg(II) and Ag(I), respectively. YES, AND, INHIBI, and XOR colorimetric logic gates were constructed on the basis of these AuNPs, which do not require targeted design or alteration of the DNA sequence. The output is colorimetric and visible to the naked eye, and the modified AuNPs aggregate in a selective manner on the basis of the addition of Ag(I) and Hg(II) (91). Metal-based DNA base pairing also has promise in molecular machines and artificial genetic circuits (92), and Liu and Sadler recently performed a computational study that supports the possibility of producing DNA nanowires by using Cu(I) ions to form multiple, adjacent base pairs (three adjacent G-Cu^+-C base pairs and two adjacent A-Cu^+-T base pairs) (62).

Expert opinion and outlook

Interactions of metal ions with DNA are an extensive research area. Multiple sites for metal ion binding exist (phosphate backbone, deoxyribose sugar, and individual bases), and even the most fundamental interactions depend on the identity of the metal ion. Redox-active metal ions are of particular interest because, besides their innate ability to bind to DNA, they can also mediate oxidative DNA damage through reactions with endogenous oxidizing agents. Metal-mediated oxidative DNA damage is implicated in various diseases and conditions, and understanding binding interactions and subsequent reactivity is required for managing or preventing oxidative damage. Future studies are expected to clarify the roles that metal ion binding and ROS scavenging play in the mechanisms by which antioxidants function, permitting more effective utilization of antioxidant activity. Specific metal-DNA interactions are also useful for enhancing the effectiveness of anticancer, antiviral, and antibacterial agents, and future advances will most likely take advantage of selective metal ion binding to DNA as a way of targeting drug therapies. Employing metal complexes to condense DNA to a nanoparticle also shows promise as a means of selective drug delivery. Metal-mediated pairing of natural and synthetic nucleobases has opened new opportunities for DNA-based metal sensors, machines, and logic gates, and further advances in this area are expected.

Highlights

- Metal-mediated oxidative DNA damage is associated with numerous diseases and clinical conditions, including cancers, diabetes, hypertension, and the aging process.
- Fe(II) reacts with H_2O_2 to produce $^{\cdot}OH$ (Fenton reaction). Cu(I), Cu(II), and Cr(III) exhibit Fenton-like behavior in the presence of H_2O_2. These reactions produce oxidative DNA damage in the form of single- and double-strand breaks and modified bases.
- 8-OH-dG is an accepted, site-specific oxidative DNA damage marker that must be produced by ROS generated from metal ions bound at or near the G base. 8-OH-dG levels are correlated closely with double-strand breaks, suggesting a similar mechanism for both types of damage.
- Several sulfur and selenium compounds function as antioxidants in metal-mediated oxidative DNA damage studies by a mechanism that involves metal ion binding.
- DNA-metal interactions are important in promoting the efficacy of anticancer, antiviral, and antibacterial drugs.
- Metal-mediated base pairing provides an alternative to naturally occurring hydrogen bonding. It results in mismatched base pairs and induces conformational changes in DNA that can be used for metal ion sensing, DNA-based machines, and logic gates where metal ions serve as the inputs.

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