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Metal Complexes Promoting Catalytic Cleavage of Nucleic Acids — Biochemical Tools and Therapeutics

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Abstract

The development of metal complexes that promote degradation of nucleic acids has garnered significant interest as a result of their broad range of potential application. This review focuses on recent progress in the design and synthesis of metal complexes as artificial nucleases that promote either hydrolytic or oxidative cleavage of nucleic acids. Illustrative examples demonstrate the versatility of artificial nucleases for in vitro applications as molecular tools to address biochemical problems, as well as their potential use as therapeutic agents. We also address future challenges for improvement and avenues for further investigation.

Introduction

Nucleic acids are a major class of biopolymers that play an important role in the central dogma; namely, DNA contains genetic information that can be transcribed into mRNA and subsequently translated to form proteins [1]. Both DNA and RNA are composed of polymeric backbones composed of phosphodiesters linked to deoxyribose and ribose, respectively [1]. The half-life for hydrolysis of DNA under physiological conditions is estimated to be over 521 year [2]; however, more rapid reaction is promoted by enzyme catalysts (nucleases), termed DNase and RNase, respectively [3]. The nuclease function is ubiquitous and involved in a variety of biological activities, including nucleic acid synthesis, recombination, regulation, processing and degradation [3]. Restriction endonucleases have been widely used in molecular cloning [3]. In addition to the natural nucleases, engineered DNase and RNase enzymes also have broad application in vitro and in vivo. For example, sequence-selective DNA strand-breaks promoted by zinc finger nucleases, transcription activator-like effector nucleases, and CRISPR/Cas systems have been employed as powerful tools for gene editing [4].

Despite the outstanding properties of conventional protein nucleases, these are not without their challenges [5]. Problems associated with protein-based nucleases include a limited pool of natural nucleases and substrate selectivity, solution instability, and a lack of membrane

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permeability. To address these problems and potentially overcome the aforementioned problems, extensive effort has been made over several decades toward developing low-molecular-weight metal complexes as "artificial nucleases" and mimics of nuclease function [6]. In this review, we briefly summarize recent progress in the design of metal complexes that mediate nuclease activity against DNA or RNA, either through hydrolytic or oxidative cleavage mechanisms. Also considered are the application of artificial nucleases, and their potential chemical and biological advantages in comparison to conventional protein-based nucleases. We also discuss the problems and challenges associated with artificial nucleases, especially for in vivo applications, and summarize design considerations for artificial nucleases that can potentially resolve those problems in vivo.

Hydrolytic and oxidative cleavage of nucleic acids

For most natural metallonucleases, divalent magnesium is the catalytic metal of choice, in part as a results of its high natural availability and high Lewis acidity, while in a few other cases divalent Zn or Ca are used [7]. Recent designs of novel catalytic DNA's (DNAzymes) that promote DNA and RNA cleavage also require Zn, Mg, Cr, or Mn as cofactors [8]. Some recent reviews have summarized the role of metal cofactors in metallonucleases and the design of DNAzymes, and so these will not be further discussed here [8]. Inspired by natural metallonucleases, a large number of studies have reported the design of strongly Lewis acidic metal complexes as artificial nucleases that promote hydrolysis of the nucleic acid phosphate backbone. These include novel Cu(II) [9,10], Cr(III) [11], Zn(II) [12], Ce(IV) [13] Zr(IV) [14], La(III) [15], Fe(III) [16], and Co(III) [17] complexes. Mechanistically, these involve the formation of a metal-phosphate intermediate that facilitates hydrolysis of the metal-bound ester (Figure 1). DNA cleavage rate is dependent on the Lewis acidity of the metal and the ease of formation of the metal-bound hydroxide nucleophile. In addition, RNA is more susceptible to hydrolysis, relative to DNA, due to the nucleophilic attack of RNA backbone by the nearby 2′ OH group that can be potentially deprotonated by metal complexes (Figure 1).

Oxidative cleavage, utilizing redox active metals, represents an alternative approach to degrade nucleic acids, often by pathways involving intermediate formation of reactive oxygen species (ROS) following electron transfer from the metal to molecular oxygen or peroxide [18]. The oxidized metal can subsequently be reduced by ascorbate or DTT, to continue formation of ROS, which typically abstract hydrogen from the deoxyribose/ribose ring followed by spontaneous cleavage of C–C and C–O bonds [18] (Figure 1). The formation of different 3′ overhang products through different C–H abstractions can be detected by use of mass spectroscopy [19].

Due to the lack of a hydrophobic environment in the substrate binding pocket of natural nucleases, small-molecule metal complexes typically exhibit slower DNA cleavage rates in solution, therefore, some strategies to enhance cleavage activities have been developed. A recent study reported the design of amphiphilic Zn-cyclen complexes conjugated to phosphocholine derivatives that, in turn, allow the formation of Zn-cyclen surface modified micelles [20]. Theses Zn-containing micelle/vehicles exhibit ~10^3–10^6 fold increase in catalytic activity for DNA hydrolysis, relative to the isolated Zn-cyclen. In addition to

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hydrophobicity, facilitating direct interaction with DNA or RNA can also play an important role in promoting effective nucleic acid cleavage. For example, Zn and Cu complexes that are linked to a cationic peptide show improved binding to DNA through electrostatic interactions and more efficient DNA cleavage [9]. A Zn complex of a diaza-crown ether was reported to exhibit more robust DNA hydrolysis relative to its copper analogues, since Zn(II) is more Lewis acidic than Cu(II) [12]. For oxidative cleavage promoted by redox active metals, an appropriate reduction potential for the $M^{(n-1)+}/M^{n+}$ couple, relative to that of the redox active coreagents (such as O_2/O_2^-, $H_2O_2/\cdot OH$) can establish more efficient redox cycling and promote rapid formation of ROS [21]. Overall, improvements in hydrophobicity, promoting contacts with the substrate, enhanced Lewis acidity (for hydrolysis) or optimizing reduction potentials (for oxidative cleavage) are all factors that have been shown to influence the catalytic cleavage reactivity of metal complexes.

Potential Applications

In contrast to protein-based nucleases that often display some measure of substrate selectivity, artificial nucleases based on metal complexes usually disregard the nucleic acid sequence and the ability to differentiate between ribose and deoxyribose rings. Consequently, such catalysts are capable of degrading a broader spectrum of substrates. The versatility of artificial nucleases has enabled development of novel molecular tools that complement conventional nucleases. Fe-EDTA and other metal complexes have been widely used as molecular probes to provide information on biological activities associated with nucleic acids, including protein-DNA/RNA interactions [22,23], the structure of DNA/RNA [24], and footprinting of nucleic acids [25] (Figure 2). For example, methidiumpropyl-EDTA-Fe has been used in the mapping of chromatin structure [26]. In these cases, the metal complex is typically used alone, to cleave the solvent-exposed sites of nucleic acids. Alternatively, metal complexes can also be linked to protein or nucleic acids to introduce substrate selectivity and promote targeted cleavage of specific sites on nucleic acids [27]. For example, the interaction between the transcription elongation factor, NusA, and nascent RNA was studied by use of Fe-EDTA-linked NusA, formed by coupling p-bromoacetamidobenzyl-EDTA (BABE) to the cysteine side chain of NuaA [28]. Similarly, Fe-EDTA has been conjugated to BvgAT194C or BvgAV148C to examine formation of the transcription complex formed by template DNA, phosphorylated BvgA, and RNA polymerase [29]. In addition to proteins, a protocol has also been reported for the site-specific incorporation of Fe-EDTA into 4-chlorophenyl-uridine of a pre-mRNA to study spliceosome assembly of pre-mRNA through RNA cleavage by the Fe-EDTA motif [24,30]. Use of metal complexes as artificial nucleases is not only complementary to other protein-based nucleases, but in some cases can also be more feasible than protein-based nucleases. Both DNA and RNA can be cleaved by artificial nucleases, while DNase and RNase, respectively, would be required if protein-based nucleases were applied. Solvent-exposed sites of nucleic acids are more accessible to these small-molecule metal complexes, relative to bulky protein-based nucleases. Metal complexes, such as Fe-BABE, can be conveniently conjugated to a specific residue of a protein or nucleic acid through chemical coupling to cysteine or nucleobases (Figure 2a), while a protein-based nuclease can only be tethered to

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the N- or C- terminus of a protein and may potentially have a negative impact on protein/nucleic acid interactions and protein folding.

In addition to in vitro biochemical studies, metal complexes that target nucleic acids can also be developed as therapeutics [31]. In fact, DNA cleavage can activate the DNA damage response signaling pathway in cells, while unrepaired DNA damage further activates the apoptotic pathway and cell death [31]. As a result, artificial nucleases that promote DNA damage can be used as anticancer agents. In fact, bleomycin, a natural product of S. *verticillus*, can promote DNA cleavage when bound to Fe or Cu, and has been approved as an anticancer agent since 1973. The mechanism of cellular selectivity of bleomycin is not well understood, but in part may reflect a defective DNA repair machinery in cancer cells, making it more difficult to identify and repair DNA lesions induced by bleomycin [32]. Similarly, a number of synthetic metal complexes have been designed that promote DNA cleavage and their anticancer activity has been broadly tested [33]. DNA breaks induced in cancer cells by metal complexes are typically confirmed by use of the TUNEL assay and/or comet assay. However, most reported examples of metal nuclease complexes exhibit very little cleavage selectivity. In contrast to other metal complexes that lack selectivity, metal complexes targeting specific DNA structures and sequences may improve drug efficacy and mitigate side effects, such as the design of a Cu complex that targets G-quadruplex telomeric DNA (Figure 3a) [34]. The incorporation of a G4 targeting motif to a Cu complex can enhance cleavage selectivity against G-quadruplex structures, relative to duplex structures. In turn, G-quadruplex-targeting metal complexes should exhibit improved cell selectivity due to the increased formation of G-quadruplex during S-phase DNA synthesis and the up-regulated synthesis of DNA in cancer cells [35]. In fact, the designed G-quadruplex-targeting Cu complexes have been shown to shorten telomere length in cancer cells through DNA cleavage, representing a novel mode of drug action that differs from bleomycin and other nonselective metal complexes [34].

In addition to anticancer therapeutics, DNA damage to other microbes may be developed into novel antibiotics or agents that inhibit biofilm formation [36]. Drug resistance against conventional antibiotics is an increasing challenge in clinical practice [37]. The main classes of antibiotics include beta-lactams, tetracycline derivatives, quinolones that target DD-transpeptidases, 16S rRNA, and DNA helicases, respectively. Therefore, DNA cleavage by metal complexes may provide an alternative target and mechanism that differs from those identified with conventional antibiotics and provide new opportunities to circumvent drug resistance. Nanoparticles surface-coated with Ce(IV) have been reported to degrade extracellular DNA (eDNA) and inhibit the growth of biofilm (Figure 3b) [38].

Nucleic acids of viruses represent a novel drug target susceptible to artificial nucleases [39]. Metal complexes that function as selective artificial nucleases, targeting HIV RRE (Rev response element) RNA, HCV SLIIB RNA, and HCV SLIV RNA have been described. To design a selective metal complex, the RNA cleaving motif is incorporated into a selective RNA binding motif, the TRQARRNRRRRWRERQR peptide for RRE [40,41], a YrFK peptide for SLIIB [42,43], and LaR2C peptides derived from La Protein for SLIV [44]. Selective cleavage of RNA is confirmed by use of MS, implying a cognate interaction between metal complex and substrate RNA that should be ascribed to RNA recognition by

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the targeting domain. Moreover, cellular replicon assays support the decrease of HCV RNA in cells following treatment with such complexes, consistent with intracellular RNA cleavage as the mode of action [42–44].

Challenge and future directions

Metal complexes have seen wide application as molecular tools for in vitro studies of a variety of biochemical problems. In vivo applications are less evident and represent an area for further exploration. Application of metal complexes that target disease-associated DNA/RNA as potential therapeutic agents should enjoy a promising future [45]. However, most metal complexes reported in current literature exhibit low substrate selectivity, and the potential for off-target activity, low efficiency in mediating chemistry, and the potential for damage to other biomolecules will result in low efficacy and side effects unless significant improvements in, and consideration of, substrate targeting are made. Approaches have been illustrated in recent works that describe applications of metal complexes to promote oxidative damage/cleavage to proteins and other metabolites, such as saccharides [46,47]. Therefore, the need for substrate selectivity becomes critically important, and the introduction of a substrate-binding moiety to designed metal complexes may improve substrate selectivity. Aside from the issue of cellular delivery and lifetime, other problems more pertinent to the coordination chemistry of such metal complexes will also require attention for cellular or in vivo application. The potential for metal dissociation (kinetic and thermodynamic lability) has also engendered anxiety concerning metal toxicity and has led to disfavor for therapeutic application of metal complexes. In addition to stability, chelate ligands used to develop metal complexes should also exhibit selectivity for the desired metal, since biologically-relevant metals, such as Ca (1.2–1.43 mM, serum) [48] and Mg (0.75–0.95 mM, serum) [49], may competitively replace the metal of choice. These problems are not insignificant and will provide ample opportunity for creativity in the design and study of the next generation of metal complexes that promote catalytic cleavage of nucleic acids.

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•• of outstanding interest

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Highlights

- New catalytic metal complexes as synthetic nucleases
- Surface adhesion in micelles and nanoparticles enhances nuclease activity
- Incorporation of a targeting motif improves selectivity and catalytic activity
- Applications in biotechnology and as therapeutics are summarized

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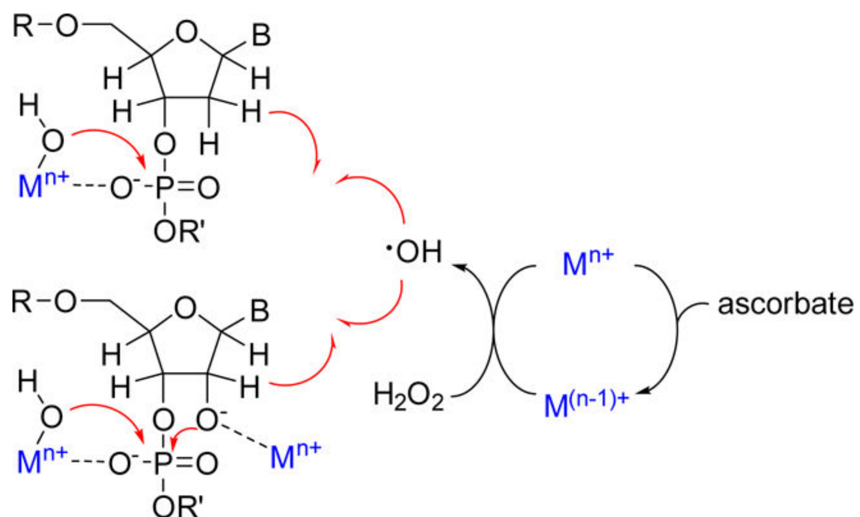

Figure 1.

Summary of hydrolytic and oxidative cleavage pathways for nucleic acids, promoted by metal complexes.

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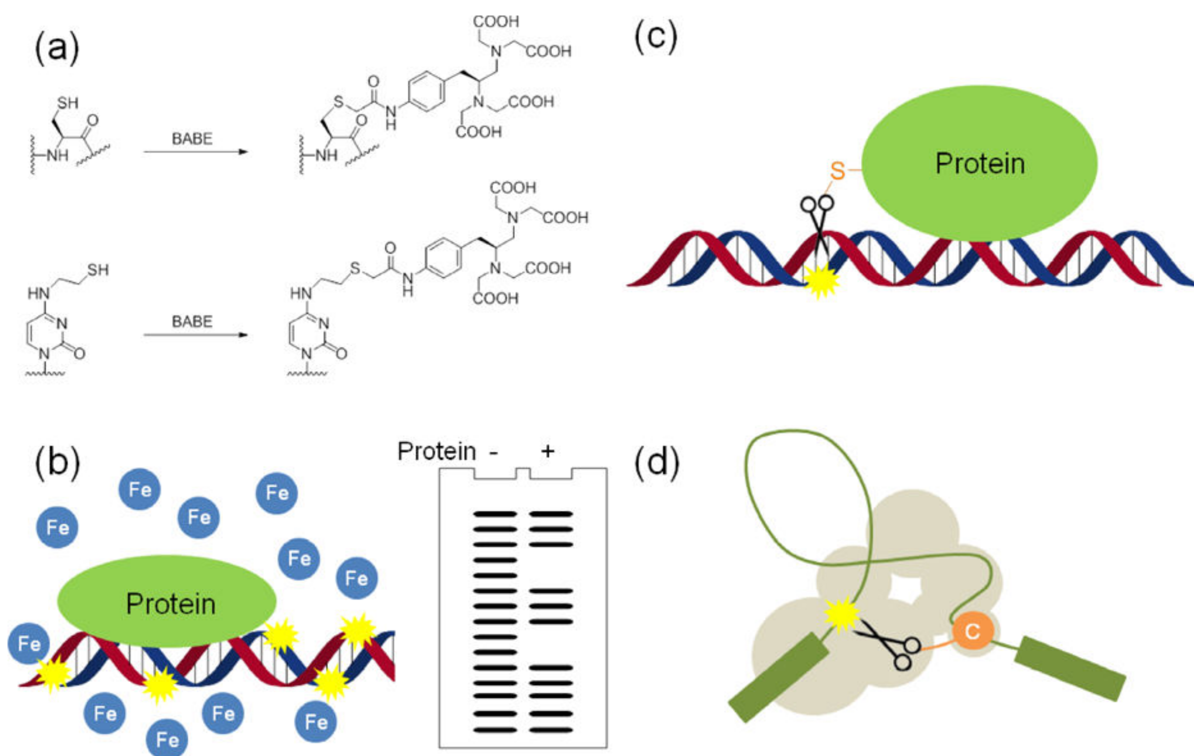

Figure 2.

Examples of the application of metal complexes as molecular tools to study DNA/RNA. (a) Incorporation of BABE into cysteine or N4-modified cytosine. (b) Solvent-exposed sites of DNA studied by metal complexes. (c) DNA-protein interaction revealed by site-selective cleavage. (d) Structure of RNA mapped by metal complexes (modified from reference [24]).

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Figure 3.
(a) A G-quadruplex-targeting Cu complex as an anticancer agent. (b) Ce-coated gold nano particles inhibiting biofilm formation