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Zinc Finger Proteins as Potential Targets for Toxic Metal Ions: Differential Effects on Structure and Function

ANDREA HARTWIG

ABSTRACT

Zinc finger structures are frequently found in transcription factors and DNA repair proteins, mediating DNA–protein and protein–protein binding. As low concentrations of transition metal compounds, including those of cadmium, nickel, and cobalt, have been shown to interfere with DNA transcription and repair, several studies have been conducted to elucidate potential interactions of toxic metal ions with zinc-binding protein domains. Various effects have been identified, including the displacement of zinc, *e.g.*, by cadmium or cobalt, the formation of mixed complexes, incomplete coordination of toxic metal ions, as well as the oxidation of cysteine residues within the metal-binding domain. Besides the number of cysteine and/or histidine ligands, unique structural features of the respective protein under investigation determine whether or not zinc finger structures are disrupted by one or more transition metals. As improper folding of zinc finger domains is mostly associated with the loss of correct protein function, disruption of zinc finger structures may result in interference with manifold cellular processes involved in gene expression, growth regulation, and maintenance of the genomic integrity. Antioxid. Redox Signal. 3, 625–634.

INTRODUCTION

ZINC plays an important role in many biochemical reactions. Up to now, several hundred zinc-dependent enzymes and proteins have been identified, with increasing tendency. By exerting catalytic as well as structural functions, zinc is involved in catalysis of metabolic pathways, macromolecular synthesis, as well as the regulation of gene expression and DNA repair (17). One important class of zinc-containing macromolecules is the so-called zinc finger proteins, where zinc complexes four cysteines and/or histidines, thereby folding a protein domain involved in DNA–protein, but also in protein–protein, interactions. Since their first description in 1985, many proteins with zinc finger structures have been identified, and it is estimated that ~1% of all mammalian genes encode zinc finger proteins (35). The "classical" type first described for transcription factor IIIA (TFIIIA) uses a zinc ion complexed to two cysteines and two histidines (Cys_2His_2 type) (39). Structural analyses revealed a two-stranded antiparallel β-sheet including the two cysteine residues, a turn, and an α-helix where the two histidine residues are located (33). Upon zinc binding, three conserved hydrophobic residues are brought together to form a stable structural domain. Thus, within the 30 amino acids present in one zinc finger motif, only seven residues and the spacing between them are conserved. DNA contact is finally mediated by three

University of Karlsruhe, Institute of Food Chemistry and Toxicology, Karlsruhe, Germany.

amino acids from the α-helix contacting three adjacent bases in DNA. Within transcription factors, finger motifs with different triplet specificities are combined in a modular fashion to provide specific recognition of longer DNA sequences (30). Besides this classical type found in many transcription factors including Sp1, the nerve growth factor I-A (NGFI-A), and the Wilms tumor-suppressor protein WT1, several other zinc-binding domains with conserved cysteine and/or histidine residues but pronounced structural diversities, have been described (Table 1). They include the steroid receptor superfamily that contains nine invariant cysteine residues, of which eight are involved in the coordination to two zinc ions forming two separate tetrahedral metal-binding units (Cys_4 type). In contrast to the TFIIIA classical zinc finger, the two zinc-binding domains fold together, forming the hormone receptor DNA-binding domain. Well known examples are the estrogen receptor (ER), the glucocorticoid receptor (GR) as well as the thyroid (TR), retinoic acid (RAR) and vitamin D3 (VDR) receptors (for reviews, see 4, 22). Another family of zinc-binding proteins includes those containing one or more sequences where zinc is complexed to three cysteines and one histidine (Cys_3His_1 type). This motif is found in some retroviruses and may be involved in RNA packaging, but also in some DNA-binding proteins; in general, it appears to be utilized for recognition of single-stranded nucleic acids (4). Finally, a new group of zinc finger proteins discovered recently are so-called RING finger proteins. They contain a zinc-binding motif where two zinc ions bind to six conserved cysteines and one histidine, stabilizing a structure involved in DNA binding, but also in protein–protein or protein–membrane interactions (for review, see 22). Examples are ubiquitin-conjugating proteins, including Mdm2 involved in p53 degradation (19). In addition to transcription factors, different zinc-binding motifs have been discovered in DNA repair enzymes. Thus, the CCHC type of zinc complexation is also present in poly(ADP-ribose) polymerase (PARP) and p53 involved in DNA repair and cell-cycle control, respectively, whereas the Cys_4 zinc finger has been found in DNA damage recognition proteins during nucleotide excision repair (see below).

Several important questions concern the evolutionary choice and specificity of zinc in these structures. Why is zinc preferred by nature over other trace elements? Are the functions of zinc finger proteins strictly dependent on zinc or can other metals substitute for it? If so, what are the biological consequences of metal replacement? Are zinc finger structures targets for toxic metal compounds, either by displacement of zinc or by redox reactions catalyzed by transition metals? Are there general predictions possible for the respective types of zinc fingers? These questions are of major importance, because toxic and/or carcinogenic metal compounds have been shown to interfere with DNA transcription and repair at low concen-

Table 1. Zinc Finger Motifs, Representative Proteins, and Their Biological Functions

Zinc finger motif	*Representative proteins*	*Biological functions*
Cys_2His_2	TFIIIA, Sp1, NGFI-A	Gene regulation
	WT1	Tumor suppressor protein
Cys_4	ER, GR, TR, RAR, VDR	Receptor proteins, gene regulation
	XPA, Fpg	DNA repair
Cys_3His_1	Retroviral nucleocapsid proteins, including Rous sarcoma virus, Rauscher murine leukemia virus	RNA packaging
	PARP	DNA repair, apoptosis
	p53	Cell-cycle control, tumor suppressor protein
RING finger	BRCA-1	DNA repair
	Mdm2	Ubiquitin protein ligase, p53 regulation

For references, see text.

trations (6, 26). First addressed by Sunderman and Barber back in 1988 (52), these aspects were elucidated by different groups and different approaches, and the results will be summarized in the following sections.

ROLE OF ZINC IN ZINC FINGER STRUCTURES AND METAL SPECIFICITY DETERMINED BY MODEL ZINC FINGER DOMAINS

As a common feature of all metal-binding protein motifs described above, the zinc ion does not directly interact with DNA, but instead is required for protein folding enabling DNA–protein or protein–protein interactions. For example, circular dichroism studies on TFIIIA indicated that the zinc finger domain is relatively unstructured in the absence of metal ions and that protein folding is coupled to metal binding (20). In the case of transcription factors and DNA repair proteins, the absence of metal ions leads to loss in DNA-binding capacity (see below).

One important question relates to the specificity of zinc binding in the different types of zinc finger structures as compared with that of other metal ions. In the absence of zinc, other transition metals are able to bind to zinc finger domains as well. For example, Co(II) has been frequently used as a spectroscopic probe for zinc sites because Co(II) complexes exhibit d → d transitions in the visible region, as well as charge transfer transitions in the UV region, whereas Zn(II) has no transitions in the visible region of the electromagnetic spectrum. Nevertheless, in the case of TFIIIA, titrations of Zn(II) to the Co(II) peptide complex revealed that zinc ions are bound about three orders of magnitude more tightly as compared with cobalt ions (Table 2). The relative affinities of TFIIIA for Co(II) and Zn(II) were discussed to be due to free energy changes related to the transition from an octahedral hexaquo complex to the tetrahedral peptide environment. Whereas Co(II) loses ligand-field stabilization energy (LFSE) upon transition from an octahedral site in water to the tetrahedral site in the metal-binding domain of the protein, no ligand field stabilization occurs in the case of Zn(II) as a closed-shell ion, resulting in specific Zn(II) binding to tetrahedral sites. A loss of LFSE should also apply for other transition metals like Fe(II) and Ni(II), suggesting the exclusion of redox-active metal ions from zinc finger structures (5). This aspect was systematically addressed by Krizek and Berg (31), who re-

Table 2. Dissociation Constants of Different Zinc Finger Motifs Containing Diverse Metal Ions

Protein or polypeptide	*Dissociation constants (M)*	*Reference*
Consensus zinc finger peptide		
CP-1 (Cys_2His_2)	K_d^{Zn}: 5.7×10^{-12} K_d^{Co}: 6.3×10^{-8} K_d^{Cd}: 2.0×10^{-9} K_d^{Ni}: 1.6×10^{-6} K_d^{Fe}: 2.5×10^{-6}	14, 15
CP-1 (CCHC) (Cys_3His_1)	K_d^{Zn}: 3.2×10^{-12} K_d^{Co}: 6.3×10^{-8} K_d^{Cd}: 6.4×10^{-12}	
CP-1 (CCCC) (Cys_4)	K_d^{Zn}: 1.1×10^{-12} K_d^{Co}: 3.5×10^{-7} K_d^{Cd}: 4.0×10^{-14}	
TFIIIA (Cys_2His_2)	K_d^{Zn}: 1.0×10^{-8} K_d^{Ni}: 2.3×10^{-5} K_d^{Cd}: 2.8×10^{-6}	16
Rauscher murine leukemia virus (Cys_3His_1)	K_d^{Zn}: 1×10^{-12} K_d^{Co}: 2×10^{-8}	57
Estrogen receptor DNA-binding domain (Cys_4)	K_d^{Zn}: 6.6×10^{-9} K_d^{Co}: 7.2×10^{-7} K_d^{Cd}: 4.8×10^{-9}	24

constructed zinc finger domains by evaluating conserved regions of known amino acid sequences. They applied a synthetic 26-amino acid peptide based on the consensus sequence of 131 zinc finger Cys_2His_2 domains [CP-1(CCHH)], as well as sequence variants where the metal-binding histidines were changed to cysteines [CP-1(CCHC) and CP-1(CCCC)]. In principle, all of the peptides bind metal ions like Co(II), Cd(II), Fe(II), and Ni(II). With respect to Co(II), dissociation constants were three to five orders of magnitude lower for Zn(II) as compared with Co(II) for all three peptides, which may be explained by ligand-field stabilization effects described above. Ni(II) and Fe(II) were bound with lower affinity as compared with Zn(II); nevertheless, binding of Ni(II) caused small distortions away from tetrahedral geometry, leading to higher affinity as would be expected from LFSE effects. In the case of Cd(II), hard–soft acid–base effects were important determinants: whereas Zn(II) was preferred in CP-1(CCHH), the affinity for Cd(II) markedly increased by three and five orders of magnitude, respectively, with the number of cysteine ligands, resulting in equal affinities of CP-1(CCHC) for both metals and a clearly preferential binding of Cd(II) over Zn(II) in the case of CP-1(CCCC) (31, 32). Yet metal exchange reactions in naturally occurring zinc finger proteins appear to be more complex and difficult to predict.

COMPETITION BETWEEN ESSENTIAL AND TOXIC METAL IONS IN ZINC FINGER TRANSCRIPTION FACTORS

Concerning the effects of toxic metal ions on the activity of zinc finger proteins, some data are available for transcription factors (Table 3). With respect to the classical Cys_2His_2 type, metal replacement studies have been performed by using TFIIIA, transcription factor Sp1, metal-response element-binding transcription factor 1 (MTF-1), as well as Tramtrack transcription factor (TTK). Even though the affinities of TFIIIA were two and three orders of magnitude higher for zinc as compared with cadmium and nickel, respectively (37), DNA binding was shown to be inhibited at nanomolar concentrations of Cd(II). This discrepancy could be due to the interaction of Cd(II) with noncoordinating cysteines in some of the zinc fingers, leading to structural alterations of the protein (25). Sp1 belongs to a growing family

Table 3. Examples for Functional Interactions by Toxic Metal Ions with Zinc Finger Proteins

Zinc finger protein	*End point*	*Metal ion*	*Concentration (μM)*	*Reference*
TFIIIA	DNA binding	Cd^{2+}	0.1	17
	DNA binding	Al^{3+}	3	
Sp1 synthetic zinc finger peptide	DNA binding	Cd^{2+}	5.5	21
		Pb^{2+}	37	
		Hg^{2+}	90	
ER	DNA binding	Ni^{2+}	Metal-reconstituted protein	24
		Cu^{2+}		
Fpg	Repair activity on oxidatively damaged isolated DNA	Hg^{2+}	0.05	39
		Cu^{2+}	5	
		Cd^{2+}	50	
XPA	Damaged DNA binding	Co^{2+}	50	39
		Cd^{2+}	100	
		Cu^{2+}	100	
		Ni^{2+}	200	
p53	DNA binding of purified murine p53	Cd^{2+}	8	51
	DNA binding in human breast cancer MCF7 cells	Cd^{2+}	20	

If not stated otherwise, all results were derived from cell-free systems.

of highly related zinc finger transcription factors for RNA polymerase II. It contains a DNA-binding domain at the C-terminus composed of three zinc finger motifs, which bind to GC-rich binding sites found in >1,000 promoters, thereby regulating cell proliferation, differentiation, apoptosis, metabolism, and secretion (18). Sp1 DNA binding is diminished in the absence of zinc, but was found to be recovered in the presence of Hg(II), Pb(II), Cd(II), Co(II), and—to lesser extents—in the presence of Ni(II) or Mn(II). Interestingly, the DNA sequence preference of Sp1 was altered in the case of Ni(II)-substituted Sp1 (41). Nevertheless, when zinc-reconstituted Sp1 was exposed to any one of the above-mentioned metals, DNA binding was impaired by all of the above mentioned metals, perhaps due to the formation of mixed-ligand complexes within the zinc fingers (47, 55). In TTK, however, substitution of zinc by cadmium disrupted the ordered secondary structure normally displayed by the zinc-bound form and inhibited its ability to bind DNA (50). Finally, DNA binding of MTF-1 derived from mammalian cell extracts was activated by Zn(II), but not by other transition metals (7). The interaction of toxic metals with the ER has been investigated mainly by Sarkar and co-workers (51). As stated above, two zinc atoms are each coordinated to four cysteine residues; this zinc-binding domain is essential for interaction with its cognate DNA sequence. DNA-binding activity was lost upon removal of zinc, but could be reconstituted by the addition of Cd(II), Co(II), and Fe(II). Ni(II) and Cu(II) were able to displace Zn(II), but did so unproductively. Relative affinities were found to be copper > cadmium > zinc > cobalt > nickel (46, 51). One explanation for the diminished DNA-binding activity of the copper-containing form of the ER is the metal ion-specific alterations in protein conformation as reported by Hutchens and Allen (27). Recently, the retroviral-type (Cys_3His_1) zinc finger has been investigated spectroscopically with respect to metal binding. The native two-zinc-finger protein fragment binds Co(II), Ni(II), and Cd(II) in a tetrahedral coordination (13), but no functional analyses have been conducted.

COMPETITION BETWEEN ESSENTIAL AND TOXIC METAL IONS IN ZINC FINGER DNA REPAIR PROTEINS

Even though most zinc finger structures have been described as DNA-binding motifs in transcription factors, they have also been identified in several DNA repair enzymes. As stated above, compounds of the carcinogenic metals nickel, cadmium, cobalt, and arsenic have been shown previously to inhibit nucleotide excision repair (NER) and base excision repair (BER) at low, noncytotoxic concentrations (26). This raises the question whether zinc finger structures in DNA repair enzymes are particularly sensitive toward carcinogenic and/or toxic metal compounds. Cys_4-type metal-binding domains are present in the bacterial UvrA protein (42), as well as in the mammalian proteins xeroderma pigmentosum A (XPA) (53) and replication protein A (RPA) (29), all of which are involved in NER and essential for DNA damage recognition. The same complexation pattern is present in the bacterial formamidopyrimidine DNA glycosylase (Fpg) protein mediating the removal of oxidative DNA base modifications (43). Homologous Cys_3His_1 metal-binding domains are found in PARP and ligase III. Whereas PARP is thought to act as a sensor of DNA single-strand breaks, ligase III has been proposed to displace the DNA-binding domain of PARP, allowing itself and other repair proteins access to the lesion during BER (36). Cys_3His_1 zinc coordination is also present in the metal-binding domain of the tumor suppressor protein p53; upon activation in response to stress, the zinc finger mediates high affinity for specific DNA sequences (14). Finally, the breast and ovarian cancer susceptibility gene BRCA 1 encodes a RING finger protein (49), required, for example, for transcription-coupled repair of oxidative DNA damage (21). However, up to now, only little is known concerning the interaction of toxic metal ions with zinc finger DNA repair enzymes and the functional implications (Table 3).

One zinc finger protein investigated with respect to metal specificity is the bacterial Fpg protein. Fpg is a glycosylase initiating BER in *E. coli*. It recognizes and removes some oxida-

tive DNA base modifications, including the premutagenic 7,8-dihydro-8-oxoguanine (8-oxoguanine). The enzyme combines the function of a glycosylase, an apurinic/apyrimidinic lyase, and a 5′-terminal deoxyribosephosphate excising activity, thus converting the DNA base damage into single-strand breaks (8, 54). DNA binding is mediated by a single zinc finger domain in the C-terminal region, where zinc is complexed by four cysteines. Substitution of any cysteine in the "zinc finger" destroys DNA-binding capacity, as well as enzyme function as a whole (43). With respect to metal binding, O'Connor *et al*. (43) reported the displacement of radioactive zinc in the Fpg protein by Hg(II), Cu(II), or Cd(II). Recently, detailed studies conducted in our laboratory revealed that the addition of Ni(II), Pb(II), As(III), or Co(II) did not affect the activity of the Fpg protein significantly. In contrast, the enzyme was inhibited in a dose-dependent manner by Cd(II), Cu(II), or Hg(II), with increasing efficiencies. Simultaneous treatment with Cd(II) or Cu(II) and Zn(II) partly prevented the inhibitions, whereas no protection was observed in the case of Hg(II). The latter effect may be due either to interactions with cysteine residues outside the metal-binding domain or to very high-affinity binding of Hg(II) within the zinc finger not readily reversed by Zn(II) (2, 3).

XPA consists of 273 amino acids and plays a central role in the first steps of mammalian NER, responsible for the removal of bulky DNA damage induced by many environmental mutagens. Loss of XPA function leads to xeroderma pigmentosum type A, a severe human disorder characterized by UV hypersensitivity and enhanced cancer risk. The protein contains specific binding sites for other NER proteins such as excision repair cross complementing protein ERCC1, TFIIH, and RPA and has been proposed to coordinate these factors in the preincision complex of NER (16). XPA binds specifically to damaged DNA, including lesions induced by UVC, benzo(a)pyrene, or cisplatin (1, 28, 48); its binding affinity is enhanced by the RPA protein (34). XPA contains a single zinc finger motif (10) which is part of the minimal DNA-binding domain (MBD) and where zinc is complexed to four cysteines (9). Substitution of any of these cysteines leads to a severe reduction of NER activity (40). Regarding XPA, Hg(II), Pb(II), or As(III) did not diminish its binding to a UV-irradiated oligonucleotide, whereas Cd(II), Co(II), Cu(II), and Ni(II) disturbed its DNA-binding ability. Simultaneous treatment with Zn(II) prevented largely the inhibition induced by Cd(II), Co(II), and Ni(II), but only slightly in the case of Cu(II) (2, 3). Interestingly, two studies were published very recently where the XPA-MBD had been constructed with Cd(II) or Co(II) instead of Zn(II) (11, 12). Structural investigations by different spectroscopic methods revealed a tetrahedral coordination of all three metal ions with no major distortion of XPA-MBD. In the case of Cd(II), however, an increased Cd-S bond length was observed (2.54 Å as opposed to 2.34 Å for Zn-S). Even though the authors considered the changes too small to disrupt DNA–protein interactions, our experiments show a diminished XPA-DNA binding by both Cd(II) and Co(II), supporting the importance of functional analyses of the protein in question. Taken together, the results indicate that both Fpg and XPA were inhibited by Cd(II) and Cu(II), XPA was additionally inactivated by Ni(II) and Co(II), and Fpg but not XPA was strongly affected by Hg(II). Even though other mechanisms of protein inactivation cannot be completely excluded, zinc finger structures in DNA repair proteins may be sensitive targets for toxic metal compounds; however, the results also show that even the same type of zinc finger (Cys_4) exerts its unique sensitivities.

With respect to Cys_3His_1 structures, the DNA-binding activity of p53 has been shown recently to be inhibited by Hg(II) and Cd(II) *in vitro* and by Cd(II) in cultured cells (24, 38). Furthermore, PARP activity was decreased in a human T-cell lymphoma-derived cell line by As(III) (57), and recent results from our laboratory demonstrate an inhibition of PARP by Ni(II), Co(II), Cd(II), and to some extent by As(III) in HeLa cells (M. Asmuss, S. Khandelwal, A. Pelzer, G. Jahnke, A. Buerkle, and A. Hartwig, manuscript in preparation). Nevertheless, whether or not this is due to an interaction with its zinc finger structure has to be further investigated.

INTERFERENCE BY TOXIC METAL IONS WITH REDOX REGULATION OF ZINC FINGER PROTEINS

Redox regulation has been demonstrated *in vitro* and *in vivo* to occur for several DNA-binding zinc finger proteins. It involves the reversible oxidation of accessible cysteine sulfhydryl groups mediated by changes in intracellular redox status. Examples are members of the Sp1 family (56), RPA (44), and the thyroid transcription factor 2 (15). This raises the question whether redox-active toxic metal ions may oxidatively damage the zinc finger structure, thereby releasing zinc instead of replacing it. With respect to metal ions, this aspect has not been investigated systematically yet; however, some results could be interpreted in this direction. Thus, the spectroscopic characterization of the synthetic Cys_2His_2 zinc finger CP-1 described above suggested the oxidation of the peptide by Cu(II) presumably to disulfide-linked species (31). Furthermore, the inactivation of the Fpg protein by Cu(II) was only slightly reversible by the addition of Zn(II) (3), and the disappearance of radioactive Zn(II) observed by O'Connor *et al*. (43) in Fpg could also be due to its release. Interestingly, preliminary results from our laboratory demonstrate an inactivation of the Fpg protein by oxidizing selenium compounds (Blessing and Hartwig, manuscript in preparation). Nevertheless, this aspect needs further investigation.

CONCLUSIONS AND PERSPECTIVES

In summary, it appears that most zinc finger structures are rather selective for zinc as compared with other metal ions; factors that contribute to this selectivity are LFSE in a tetrahedral complexation and hard–soft acid–base effects. The advantage of zinc over other transition metals is the lack of redox chemistry, thus

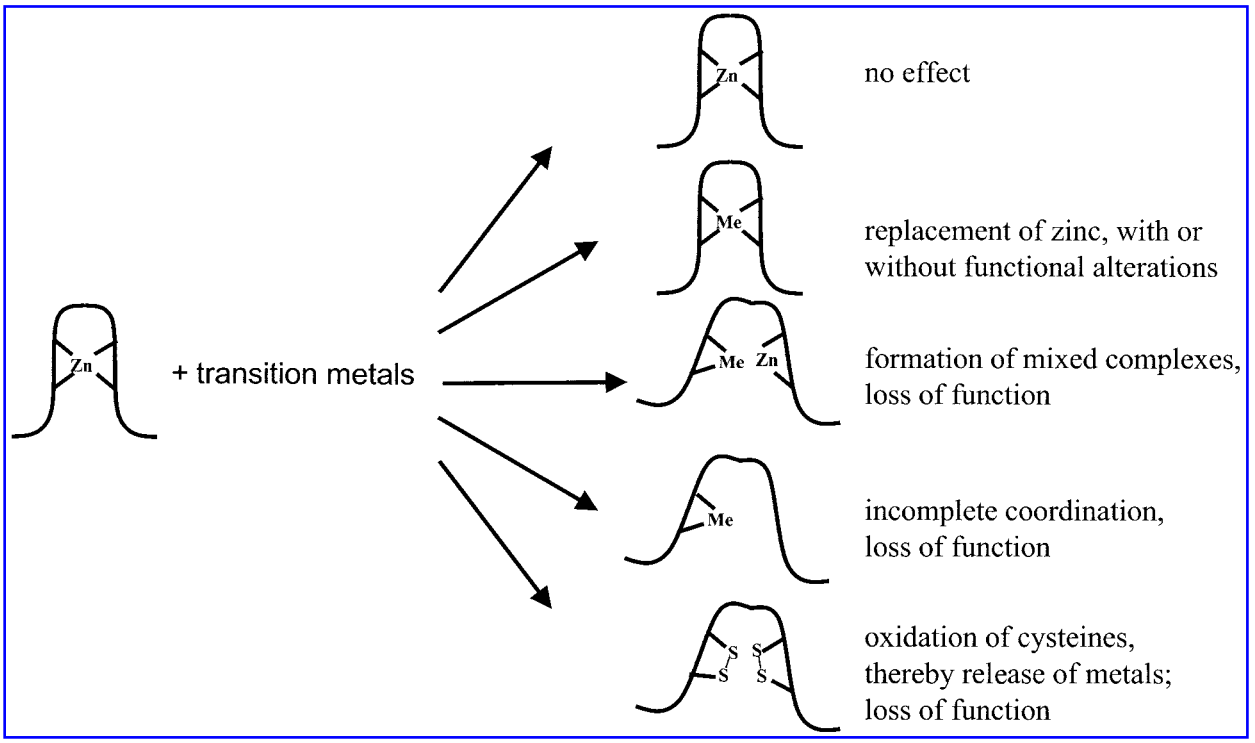

FIG. 1. Schematic representation of potential modes of interaction of toxic transition metal ions with zinc-binding structures in transcription factors and DNA repair proteins. As evident from the diverse examples described in the text, the type of interaction depends not only on the respective metal ion, but also on the zinc finger domain under investigation, because each one exerts its own structural features, resulting in different sensitivities toward toxic metal ions.

preventing redox reactions in close proximity to the DNA. However, this preference is lost in the case of Cys_4 structures, where the affinity for Cd(II) is higher as compared with Zn(II) due to its high affinity to SH groups. Consequently, Cd(II) has been shown to displace zinc and/or to disturb DNA binding, for example in the ER as well as in the DNA repair proteins Fpg and XPA. Nevertheless, interactions with toxic metal ions are not restricted to Cd(II) and not to the Cys_4-type finger. As demonstrated for Sp1, binding of other transition metals may lead to mixed ligand complexes and distortions of tetrahedral structures, thus altering DNA-binding behavior and/or sequence preference. Finally, redox-active metal ions may oxidize essential cysteines and/or other residues in zinc finger structures, thereby disturbing the metal binding domain. Thus, the data available in the literature demonstrate that zinc finger structures may be sensitive targets for toxic metal compounds, and different types of interaction have been demonstrated (summarized in Fig. 1). Yet each zinc finger protein exerts its own structural features and sensitivities toward toxic metals, and no general predictions appear to be possible. The potential relevance of structural distortions of zinc finger domains becomes evident from observations that mutations in the zinc finger region are frequently associated with clinical phenotypes of different diseases. For example, all 10 patients suffering from Denys–Dresh syndrome, a severe disease characterized by urogenital developmental abnormalities and implicated in the etiology of Wilms tumor, exerted mutations within DNA regions coding for two zinc finger motifs of WT1 (45). Similarly, replacement of any of the cysteines involved in zinc complexation in XPA leads to nearly complete loss of DNA repair activity (23). As zinc finger proteins are involved in basically all cellular processes, their inactivation may impair cell growth, differentiation, as well as cell-cycle control and DNA repair. Furthermore, the binding of redox-active metal compounds in close proximity to the DNA may lead to redox reactions bearing the danger of damaging the DNA directly. Therefore, the interaction with zinc finger structures may be one relevant mechanism of action of carcinogenic metal compounds.

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ABBREVIATIONS

BER, base excision repair; BRCA 1, breast cancer protein 1; ER, estrogen receptor; Fpg, formamidopyrimidine DNA glycosylase; GR, glucocortioid receptor; LFSE, ligand-field stabilization energy; MBD, minimal DNA-binding domain; MTF-1, metal-response element-binding transcription factor 1; NER, nucleotide excision repair; NGFI-A, nerve growth factor I-A; PARP, poly(ADP-ribose) polymerase; RAR, retinoic acid receptor; RPA, replication protein A; Sp1, transcription factor Sp1; TFIIIA, transcription factor IIIA; TR, thyroid receptor; TTK, Tramtrack transcription factor; VDR, vitamin D3 receptor; WT, Wilms tumor protein; XPA, xeroderma pigmentosum A protein.

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Address reprint requests to:
Prof. Dr. Andrea Hartwig
University of Karlsruhe
Institute of Food Chemistry and Toxicology
Postfach 6980
D-76128 Karlsruhe
Germany

E-mail: Andrea.Hartwig@chemie.uni-karlsruhe.de

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