Minireview

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Zinc Fingers and Other Metal-binding Domains*

ELEMENTS FOR INTERACTIONS BETWEEN MACROMOLECULES

Jeremy M. Berg

From the Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

Biochemical experiments in the 1970s and early 1980s implicated metal ions as important components in several gene regulatory proteins (1–3). These results foreshadowed a virtual explosion of results that has occurred since 1985 revealing the presence of small domains, structurally organized around coordinated metal ions such as zinc(II), in nucleic acid-binding and gene regulatory proteins (for selected previous reviews see Refs. 4, 45, and 70). In this review, the evidence implicating zinc as an important structural component in members of four protein classes involved in nucleic acid binding and/or gene regulation will be examined.

Interactions with Double-stranded DNA

The Zinc Finger Proteins—In 1983, Hanas *et al.* (3) reported that *Xenopus* transcription factor IIIA (TFIIIA)[1] contained multiple bound zinc ions and that these ions were required for site-specific DNA binding activity. In particular, they showed that the TFIIIA-5 S RNA complex isolated from *Xenopus* oocytes contained 2–3 zinc ions that were bound sufficiently tightly to be stable to dialysis against 5 mM EDTA. When the protein was freed of RNA by nuclease treatment, it was found to bind specifically to 5 S RNA genes. However, treatment of the freed protein with EDTA removed the zinc ions and produced a material with no detectable specific DNA binding activity. Addition of zinc to this preparation restored the specific DNA binding activity. A surprising and highly appealing explanation for this observation emerged from analysis (5, 6) of the deduced amino acid sequence of TFIIIA (7). It was discovered that the TFIIIA primary structure includes nine tandemly arrayed sequences that closely approximate the form (Tyr,Phe)-X-Cys-$X_{2,4}$-Cys-X_3-Phe-X_5-Leu-X_2-His-$X_{3,4}$-His-X_{2-6}. Furthermore, it was found that if the TFIIIA-5 S RNA complex was purified under conditions that avoided the use of potential chelating agents, 7–11 eq of zinc were present per protein molecule (6). Based on these two observations, it was proposed that each of the short sequences binds a zinc ion through the invariant cysteine and histidine residues (5, 6) to form a small structural domain which was termed a "zinc finger" (6). The validity of the basic hypothesis has been established through a variety of methods. The most direct evidence comes from x-ray absorption spectroscopic studies of the zinc sites in the TFIIIA-5 S RNA complex (8). Furthermore, studies of single zinc finger peptides indicate that these peptides fold in the presence of metal ions such as Zn^{2+} or Co^{2+} but not in their absence (9, 10).

Shortly after the analysis of the TFIIIA sequence, several additional protein sequences were deduced that were found to contain quite similar sequences. These included two putative proteins from a *Drosophila* locus termed serendipity (11), the *Drosophila* segmentation gene Krüppel (12), and the yeast transcription factor ADR1 (13). In addition, the well defined nature of the zinc finger consensus sequence, including especially the linker between adjacent zinc finger domains, has allowed a number of zinc finger-encoding genes to be intentionally cloned by hybridization (14, 15). Over the past 4 years, over 100 genes encoding one or more zinc finger sequences have been isolated and sequenced (see Ref. 16 for references).

Where it has been experimentally characterized, the activities of these proteins include sequence-specific interactions with double-stranded DNA. Thus, for yeast ADR1 (17) and SWI5 (18), *Drosophila* Krüppel (19, 20), Hunchback (19, 20), and Suppressor of Hairy Wing (21), mouse zif-268 (22), and human Sp1 (23), DNase I footprinting experiments have revealed specific binding sites. Genetic and biochemical experiments have identified the zinc finger regions of these proteins as the sites of the specific binding activities (24, 25).

Models for the structural basis of the interaction between tandem arrays of zinc finger domains and DNA have been deduced based on two similar predictions for the structure of a zinc finger domain (26, 27). Strong support for the validity of one of the predicted structures (26) has come from two-dimensional NMR studies of a single zinc finger peptide (28). The structure consists of a two-stranded antiparallel β sheet that includes the 2 cysteine residues, a turn, and then a helix that includes the 2 histidine residues. This structure is shown in Fig. 1. The observation that the amino and carboxyl termini of this structure are well separated from each other leads to the strong suggestion that a zinc finger protein wraps around the DNA helix to which it binds, perhaps with the helical portion of the structure lying in the major groove of the DNA. This is illustrated in Fig. 2. This type of model suggests a ratio of 3 base pairs per zinc-binding domain (4, 27, 45, 71). Examination of models of this sort reveals that the domains look rather more like "sausage links" running parallel to the direction of the body of the protein than they look like "fingers" (that would project perpendicular to the body of the protein). Thus, in our laboratory we often use the term "zinc links." Testing of this model will require extensive biochemical experimentation including the determination of the structure of a complex containing a zinc finger protein bound to its target nucleic acid. Such structures have elucidated the architecture of DNA complexes of proteins containing the "helix-turn-helix" motif in exquisite detail in recent years (29–31).

The Steroid Receptor and GAL4 Families—Several other classes of double-stranded DNA-binding proteins have been discovered that contain different patterns of cysteine residues. These include the steroid receptor superfamily that contains 9 invariant cysteine residues and the GAL4 family that contains 6 invariant cysteine residues. For members of each class, direct evidence has been obtained for the importance of bound metal ions such as zinc(II) for site-specific DNA binding. A 150-amino acid fragment of the glucocorticoid receptor expressed in *Escherichia coli* has been shown to bind 2 eq of zinc or cadmium (32). X-ray absorption spectra are consistent with each zinc atom being coordinated to four sulfur atoms from cysteinate at a distance of 2.32 Å (32). Furthermore, the presence of bound metal ions was shown to be required for

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[1] The abbreviation used is: TF, transcription factor.

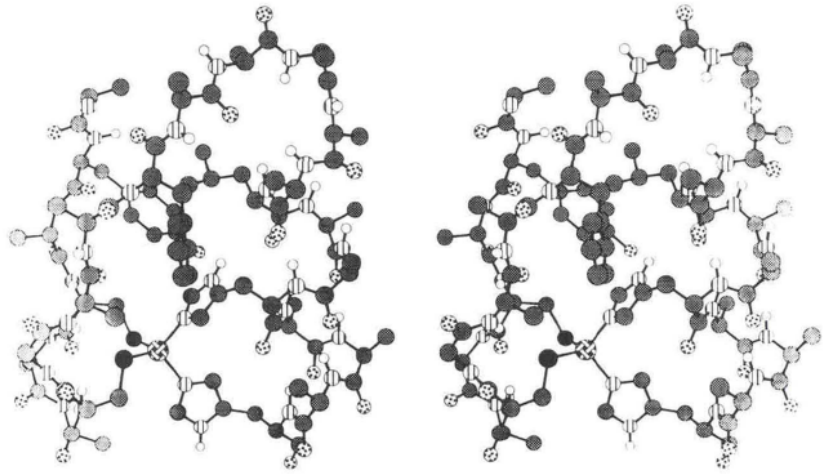

FIG. 1. **A stereo pair showing the predicted structure of a zinc finger domain.** Only β carbons are shown for the side chains except for the metal-binding and most conserved hydrophobic residues. The atom types are indicated as carbon (*gray*), hydrogen (*white*), oxygen (*speckled*), nitrogen (*striped*), and zinc (*checked*).

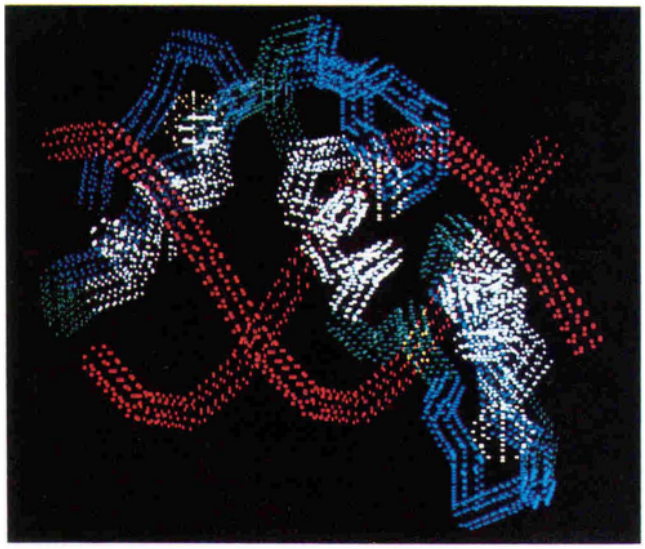

FIG. 2. **A model for the structure of three tandem zinc finger domains bound to one turn of B form DNA.** The helical regions are shown in *white*, the β sheet in *blue*, the remainder of the polypeptide backbone in *green*, the zinc ions in *yellow*, and the DNA backbone in *red*. The helices lie in the major groove of the DNA.

specific DNA binding using gel mobility shift and DNase I footprinting assays (32). These results are consistent with 8 of the 9 invariant cysteines being involved in coordination to the two metal ions to form two separate tetrahedral metal-binding units. The two metal-binding domains play different roles in DNA binding and receptor function (for references see Berg (33)). For the GAL4 family, a variety of evidence indicates that metal binding is required for specific DNA binding. The first data to be obtained came from a genetic experiment (34). Mutants were isolated based on their inability to grow on galactose as the sole carbon source. Mutation of a proline residue to leucine resulted in a strain that was not able to grow on galactose except if additional zinc was added. This suggests that the sequence change results in a protein that has a decreased affinity for zinc compared with the wild type. More direct biochemical evidence has been obtained on fragments of GAL4 produced in *E. coli*. Carey *et al.* (35) reported that a fragment of GAL4 containing residues 1–147 did not specifically bind DNA when treated to remove bound metal ions and that DNA binding activity could be restored by treatment with Zn^{2+}, Cd^{2+}, or Hg^{2+}. Pan and Coleman (36) prepared a similar fragment and showed that it contained 1–1.5 eq of zinc as isolated. Cadmium could be substituted for zinc by removal of the zinc by treatment with EDTA at low pH followed by the addition of cadmium (36). Interestingly, ^{113}Cd NMR indicated the presence of two distinct cadmium sites, both of which appeared to be bound by at least three sulfur-containing ligands (36). Thus, although more data need to be obtained, it appears possible that this family of proteins has a binuclear $Zn_2(Cys)_6$ center with two bridging cysteinate ligands and two slightly different metal sites. Molecules with such a structure have previously been synthesized (37). It is very important to note that there is no evidence that the steroid receptor and GAL4 classes are structurally related to one another or to the TFIIIA family in any detailed way although these classes are often grouped together as zinc finger proteins.

Interactions with Single-stranded Nucleic Acids

Retroviral CCHC Box Proteins—Shortly after the discovery of the pattern of cysteine and histidine residues in TFIIIA, a systematic search method was developed for identifying patterns of cysteine and histidine residues in proteins of known sequence (38). Prominent among the proteins discovered by this method are the retroviral nucleocapsid proteins. Some viruses, typified by Rauscher murine leukemia virus, contain a single sequence of the form Cys-X_2-Cys-X_4-His-X_4-Cys (hereafter, a CCHC box). Others, such as human immunodeficiency virus, contain two such sequences. The presence of this recurring sequence in these proteins had been previously noted (39) although its potential as a metal-binding site had not been discussed. The presence of bound metal ions in these proteins has been controversial (40, 41). The nucleocapsid protein from Rous sarcoma virus purified by the standard method was found not to contain significant quantities of bound metal ions (40). Furthermore, addition of zinc to these preparations did not affect either the spectroscopic properties of this protein nor its behavior in a nonspecific single-stranded nucleic acid binding assay (40). However, further characterization of this material revealed the presence of a disulfide bond (42). This underscores a general problem with the proteins that are the subject of this review. Because of the high density of cysteine residues, they are often quite sensitive to air oxidation and inactivation, particularly in the absence of sufficient quantities of appropriate metal ions. Studies with synthetic peptides derived from several viruses (41, 43) and with synthetic protein from Rauscher murine leukemia virus (44)[2] have revealed that, in appropriately reduced forms, materials containing this pattern of cysteine and histidine residues do, indeed, bind metal ions such as zinc and cobalt with high affinity. Moveover, the presence of such

[2] L. M. Green and J. M. Berg, submitted for publication.

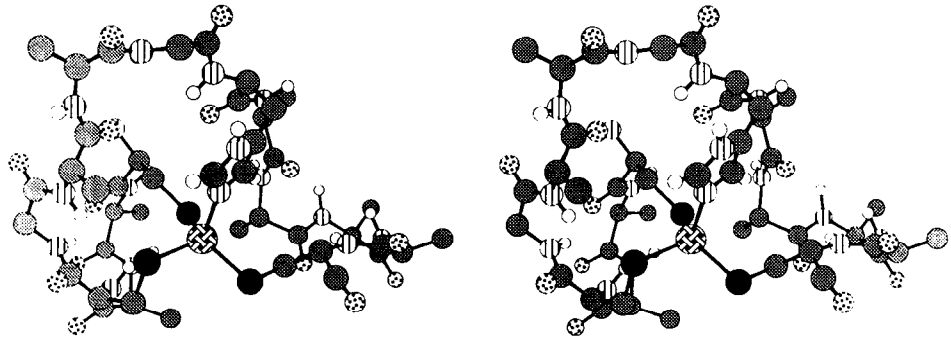

FIG. 3. **The stereo pair showing the structure of a retroviral CCHC box peptide bound to zinc.** Only β carbons are shown for the side chains except for the metal-binding residues. This figure is based on coordinates kindly provided by Professor Michael Summers.

ions has profound effects on the structure of the metal-binding domain. This has been most directly determined by the NMR studies of Summers and co-workers (43). They have now determined the structure of one such retroviral CCHC box domain quite precisely by NMR methods (46). This structure is shown in Fig. 3.

The role of these proteins in the viral life cycle has recently been probed by site-directed mutagenesis. The CCHC box regions of several viruses have been mutated in such a way as to remove entire 14-amino acid boxes (47) or to change individual residues (40, 48, 49). A very interesting phenotype is often observed. Virus particles are released from infected cells, but these are not infectious and further characterization reveals that they lack viral RNA. This phenotype is observed for mutants in which the metal-binding residues themselves have been modified. For some other changes in the CCHC box region, RNA is present inside the virus particle, but it is not the viral genome but rather some other RNA species present in the cell. These observations suggest that the CCHC box proteins play a central role in RNA packaging, perhaps recognizing a specific packaging signal in the viral RNA (41, 48). The most commonly utilized assay for these proteins *in vitro* has been a nonspecific single-stranded nucleic acid binding assay. A variety of evidence, including the observation that modification of the cysteine residues via alkylation (50) or oxidation (51) does not affect the behavior of the proteins, suggests that this assay does not reflect the full biological activity of these proteins. More recently, studies with synthetic Rauscher murine leukemia virus protein have revealed that zinc binding also does not significantly affect behavior in this assay (44). It seems likely that a specific protein-viral RNA interaction is yet to be discovered. One of the features expected for this interaction is that it should be metal-dependent. Interestingly, removal of the zinc from TFIIIA results in loss of its specific interactions with DNA but increases its affinity for single-stranded nucleic acids (52).

The CCHC box is not completely limited to retroviruses. Other retrovirus-like elements such as the yeast transposable element copia (53) contain CCHC box sequences. Furthermore, it had been discovered that cauliflower mosaic virus, a DNA virus that goes through a reverse transcription step, has one CCHC box sequence within its sequence (54). Another exciting discovery reported recently involves the cloning of a human gene that encodes a protein involved in recognition of a DNA sequence that had been implicated in sterol-mediated gene repression (55). This protein was found to contain seven CCHC box sequences. It was discovered that the protein specifically binds to one of the single strands of the binding site but not to the other nor to the double-stranded form. This provides further evidence that the CCHC box motif is an element utilized for recognition of single-stranded nucleic acids.

Protein-damaged DNA Interactions

E. coli uvrA and Mammalian Poly(ADP-ribose) Polymerase—Two proteins involved in specific binding to damaged DNA have been found to contain sequences which appear to be capable of forming metal-binding domains. The first of these systems is the *E. coli* uvrA protein. This is the component of an excision/repair system that recognizes the damaged site (56). This 940-amino acid protein contains two sequences of the form Cys-X_2-Cys-$X_{19,20}$-Cys-X_2-Cys (57). The protein binds two zinc ions, and recently reported x-ray absorption spectroscopic studies are entirely consistent with tetrahedral four-cysteinate coordination of each zinc (58). Moveover, site-directed mutagenesis studies reveal that modification of one of the cysteine residues results in a decrease in activity in a complementation assay (58). The second system is mammalian poly(ADP-ribose) polymerase, an enzyme that catalyzes the attachment of ADP-ribose to various proteins. This activity is induced by the presence of single strand breaks on DNA (59). This protein contains two tandem sequences of the form Cys-X_2-Cys-$X_{28,30}$-His-X_2-Cys (60). It had been shown that this protein requires zinc for activity (61), and it has recently been shown that the protein does bind zinc and that this bound zinc is required for binding to nicked DNA (62). For both of these systems, much remains to be done with regard to the structure of these zinc-binding domains and to the detailed role that these domains play in the recognition of damaged DNA.

Protein-Protein Interactions

The Bacteriophage T4 Gene 32 and the Adenovirus E1A Proteins—Protein-protein interactions play an important role in many gene regulatory processes. For at least two systems, extant data indicate that metal-based domains are involved in mediating such interactions. The bacteriophage gene 32 protein (often called the helix-destabilizing protein) is a prototypical single-stranded nucleic acid-binding protein that binds cooperatively to single-stranded DNA and RNA. This protein contains a sequence of the form Cys-X_3-His-X_5-Cys-X_2-Cys that was detected by the systematic sequence search discussed previously (38). Simultaneously, Giedroc *et al.* (63) reported that it contains one atom of zinc/protein and that spectroscopic properties of the cobalt-substituted protein were consistent with binding to the sequence above. The presence of the metal ion has pronounced effects on protein stability. For example, the apoprotein is dramatically more susceptible to proteolysis than is the zinc-containing form (63). The presence of bound metal is not required for binding of the protein to nucleic acids in that the affinities of the apo- and metalloproteins for $d(pT)_8$ are within an order of magnitude of one another (64). However, bound zinc has a pronounced effect on the cooperativity of binding; the affinity of the zinc form for $d(pT)_{16}$ is over 2 orders of magnitude higher than that for the single site lattice whereas the affinity of the

apoprotein increases less than 5-fold (64). One interpretation of this observation is that the metal-binding domain mediates interactions between monomers. Recently published results support this hypothesis. Small-angle x-ray scattering results suggest that the apoprotein is monomeric whereas the zinc-containing protein is dimeric (65).

The adenovirus E1A gene encodes several proteins that play fundamental roles in transcription of other early viral genes (66). The gene produces one RNA precursor which matures to different messenger RNAs that differ in the size of the region removed by the splicing process. In particular, 12 and 13 S messages are produced which are translated into proteins that are identical at each end but differ by an internal region of approximately 50 amino acids. This region contains a sequence of the form Cys-X_2-Cys-X_{13}-Cys-X_2-Cys which was also detected by the systematic sequence search (38). Analysis of the E1A proteins produced in bacteria revealed that the larger protein contained one atom of zinc/protein whereas the smaller did not contain appreciable levels of zinc (67). Further evidence for the importance of this domain for transactivation comes from studies with a synthetic 49-amino acid peptide that corresponds to this domain (68). Microinjection of this peptide into cells leads to activation of an E1A-inducible promotor. Despite much effort, there is no strong evidence that the E1A protein binds specifically to DNA, and no common sequence element has been discovered that is common to E1A-inducible promotors (69). Thus, it appears probable that E1A acts by interacting with other proteins involved in the transcription process.

Summary and Conclusions

From the examples discussed above, it is clear that metal-binding domains play central roles in mediating interactions between proteins and many different types of macromolecules. Why are metal-binding domains utilized in this manner? What properties unite these systems? One answer is based on the thermodynamics of protein folding and on the special properties of metal ion-ligand interactions. Protein folding is driven by a variety of forces including formation of specific hydrogen bonds and ion pairs, van der Waals interactions, and the burial of hydrophobic surfaces. These interactions are necessary to overcome the large conformational entropy of the unfolded form of a protein. The binding of a metal ion introduces a series of cross-links that reduce the number of accessible conformations and, hence, the conformational entropy of a protein. Phenomenologically, it appears that metal-based domains are generally smaller than protein domains that are devoid of cross-links. This may be due to the fact that for a small domain (less than 50 amino acids) devoid of cross-links, it may not be possible to gain enough free energy from favorable interactions to overcome the conformational entropy of the unfolded form. Thus, metal binding may be a very useful process for forming bumps and ridges that extend from the surfaces of proteins that are well suited for interactions with other macromolecules.

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