



Review

Metal binding properties, stability and reactivity of zinc fingers

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ABSTRACT

Zinc fingers (ZFs) are among the most structurally diverse protein domains. They interact with nucleic acids, other proteins and lipids to facilitate a multitude of biological processes. Currently, there are more than 10 known classes of ZFs, with various architectures, metal binding modes, functions and reactivity. The versatility, selectivity and stability of these short amino acid sequences is achieved mainly by (i) residues participating in Zn(II) coordination (mostly Cys and His), (ii) hydrophobic core and ZF structure formation, and (iii) variable residues responsible for inter- and intramolecular interactions. Since their discovery, ZFs have been extensively studied in terms of their structure, stability and recognition targets by the application of various methodologies. Studies based on interactions with other metal ions and their complexes have contributed to the understanding of their chemical properties and the discovery of new types of ZF complexes, such as gold fingers or lead fingers. Moreover, due to the presence of nucleophilic thiolates, ZFs are targets for reactive oxygen and nitrogen species as well as alkylating agents. Interactions with many reactive molecules lead to disturb the native Zn(II) coordination site which further result in structural and functional damage of the ZFs. The post-translational modifications including phosphorylation, acetylation, methylation or nitrosylation frequently affect ZFs function via changes in the protein structure and dynamics. Even though the literature is replete with structural and stability data regarding classical ($\beta\beta\alpha$) ZFs, there is still a huge gap in the knowledge on physicochemical properties and reactivity of other ZF types. In this review, metal binding properties of ZFs and stability factors that modulate their functions are reviewed. These include interactions of ZFs with biogenic and toxic metal ions as well as damage occurring upon reaction with reactive oxygen and nitrogen species, the methodology used for ZFs characterization, and aspects related to coordination chemistry.

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Contents

1. Introduction	19
2. Zinc finger architecture and function	20
2.1. Historical overview	21
2.2. Discovery of the $\beta\beta\alpha$ ZF fold and its DNA recognition mode	22
2.3. Structural diversity within zinc finger domains	22
2.4. Family of $\beta\beta\alpha$ zinc fingers	22
2.5. Gag knuckle zinc fingers	23
2.6. Zinc ribbons	25
2.7. Other zinc finger-like motifs	25
2.7.1. CCCH type	25
2.7.2. CCHHC type	26
2.8. Treble clef zinc fingers	27
2.8.1. RING domains	27
2.8.2. LIM domains	28
2.8.3. FYVE domains	28

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2.8.4.	PHD domains	28
2.8.5.	B-box domains	29
2.8.6.	HIT domains	29
2.9.	Zn ₂ Cys ₆ type zinc fingers	29
2.10.	TAZ-like zinc fingers	29
3.	Stability of zinc finger complexes	29
3.1.	Definition of zinc finger stability constants	30
3.2.	Overview of methods used for determination of ZF stability constants	31
3.2.1.	Direct spectroscopic methods	31
3.2.2.	Spectroscopic reverse titrations of zinc fingers	32
3.2.3.	Potentiometry and pH-metry	33
3.2.4.	Competition with chromophoric chelating probes	34
3.2.5.	Competition with complexones	34
3.2.6.	Stability constants of ratiometric probes based on zinc fingers	36
3.2.7.	Isothermal titration calorimetry	37
3.2.8.	Choice of the best method	37
3.3.	Factors controlling zinc finger stability	38
3.3.1.	Acid-base properties of Zn(II) ligands in zinc fingers	38
3.3.2.	Effect of increased number of Cys residues in coordination sphere on ZF complex stability and metal ion selectivity	39
3.3.3.	Presence of residues other than Cys or His and lack of ligands in the coordination sphere	40
3.3.4.	Alteration in hydrophobic core and loop of ββ α zinc fingers	41
3.3.5.	Metal-coupled folding of ZF domains	42
3.3.6.	Multiple stabilizing effects in a sophisticated consensus zinc finger and highly stable domains	43
4.	Metal binding properties of zinc fingers	44
4.1.	Co(II) ion as a spectroscopic probe of Zn(II) in ZF proteins	44
4.2.	Ni(II) ion as a spectroscopic probe and damage factor of ZFs	46
4.3.	Cadmium fingers	48
4.4.	Lead fingers	48
4.5.	Copper affects structure and function of native ZFs	49
4.6.	Interaction of inorganic and organic arsenic species with zinc fingers	50
4.7.	Zinc fingers as molecular targets of antimony	50
4.8.	Gold fingers	51
4.9.	Interaction of platinum compounds with zinc fingers	52
4.10.	Iron interaction with zinc fingers	52
5.	Reactivity of zinc fingers	53
5.1.	Factors controlling ZF reactivity	53
5.2.	Protein structure alteration induced by zinc finger reactivity and modification	54
5.2.1.	Oxidation and nitrosylation	55
5.2.2.	Alkylation	56
5.2.3.	Phosphorylation and acetylation	57
5.3.	Hydrolytic properties of zinc finger complexes	59
6.	Future research directions	60
	Acknowledgements	60
	References	60

1. Introduction

Among all inorganic cofactors in biological systems, d-block metal ions are the most widespread facilitating diverse functions of proteins and their complexes. Bioinformatic studies performed on the human genome indicate that ~10% of all encoded proteins participate in Zn(II) ion binding [1,2]. This enormous contribution of zinc domains and motifs with various metal affinities encourages researchers to further investigate Zn(II) ions and their physiological role. It is commonly known that Zn(II) ions play a unique role not only in enzyme catalytic activity, but also in protein stabilization, and even facilitate folding of protein subunits [3–7]. The structural role of the Zn(II) was proposed when zinc finger (ZF) domain was found in *Xenopus laevis* transcription factor IIIA (TFIIIA) [8,9]. Further studies showed that TFIIIA zinc fingers utilize two Cys and two His residues (CCHH) coordinating the Zn(II) ion to adopt a ββ α fold with three hydrophobic residues responsible for the formation of a small hydrophobic core which offers additional stabilization of the ZF domain [10]. Over the years, the small independent TFIIIA-like zinc finger motifs with CCHH coordination of Zn(II) have been found in many other proteins with functions

related to gene expression control [9,11–14]. Even though the CCHH zinc finger motif has been found to be one of the most ubiquitous coordination sites of Zn(II), other additional classes of single and double ZFs with different coordination modes and Zn(II)-stabilized structures have also been discovered and characterized in terms of their structural stability and metal binding properties [15–20]. The huge structural and sequential diversity means that the zinc finger family is the most versatile protein domain type, representatives of which selectively interact with nucleic acids, other proteins and lipids [21–24]. The structure of the ZF domain is unique as upon Zn(II) binding coordination bonds with the metal ion are formed, providing a stable fold which in comparison to other shorter protein motifs is highly packed. In addition, in some ZF coordination spheres other amino acids such as aspartic or glutamic acids are found instead of Cys or His residues. Nevertheless, besides diversity within coordination residues all ZF domains upon Zn(II) binding are observed to adopt tetrahedral coordination whose stability depends on many factors including hydrogen bonds, hydrophobic and electrostatic interactions [25–29].

Besides the structure and relative rearrangement of zinc fingers, which are critical for intermolecular interactions, there are

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