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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 (ββα) 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.

Contents

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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 ββα 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