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Structure and function of heme proteins regulated by diverse post-translational modifications

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ABSTRACT

Heme proteins are crucial for biological systems by performing diverse functions. Nature has evolved diverse approaches to fine-tune the structure and function of heme proteins, of which post-translational modification (PTM) is a primary method. As reviewed herein, a multitude of PTMs have been discovered for heme proteins in the last several decades, including heme-protein cross-links with heme side chains (Cys-heme, Tyr-heme and Asp/Glu-heme, *etc*) or porphyrin ring (Lys-heme and Tyr-heme, *etc*), heme modifications (sulfheme and nitriheme, *etc*), amino acids cross-links between two or among multiple residues (Cys-Cys, Tyr-His, Tyr-Cys, Met-Tyr-Trp, *etc*), and amino acids modifications by oxidation, nitration, phosphorylation and glycation, *etc*. With the development of research methods and advances in research techniques, deep insights have been obtained for the formation mechanisms of PTMs, as well as their effects on the structure and function of heme proteins. Moreover, some positive PTMs have been successfully applied to create artificial heme proteins with advanced functions, whereas some negative PTMs have been regulated by rational design of inhibitors. The tremendous progress, together with those ongoing, will make it possible to rationally control the diverse PTMs of heme proteins, especially those associated with human diseases, toward our desired goals for a better life.

1. Introduction

Metalloproteins and metalloenzymes are crucial for all living systems, of which heme proteins perform diverse biological functions, including oxygen binding and delivery (e.g. myoglobin, Mb and hemoglobin, Hb), electron transfer (e.g. cytochrome *c*, Cyt *c* and cytochrome b_5, Cyt b_5), catalysis (e.g. peroxidase and cytochrome P450, CYP450) and signaling (e.g. CO sensor CooA) [1–11]. The functional diversity is closely related to various interactions between the heme and protein matrix, such as the covalent attachment of heme to protein matrix, the coordination between heme iron and axial ligands (His, Met, Cys, water, *etc*), and the hydrogen(H)-bonding interactions in the heme distal pocket. In addition to these covalent and non-covalent interactions, nature has evolved other methods to fine-tune the structure and function of heme proteins, and post-translational modification (PTM) is a primary one [12].

PTMs are the most important biological mechanisms for modulating the structure and function of proteins, which allow the cell to response to changes in external conditions or internal states [13]. More than 200 different types of PTMs have been discovered [14], and a multitude of PTMs have been investigated for heme proteins in last several decades. As reviewed herein, these PTMs involve enzymatic and nonenzymatic modifications under reductive or oxidative conditions, resulting in cross-links between the heme and protein matrix, heme modifications, cross-links between amino acids and modifications of amino acids. This review focuses on the formation mechanisms of such PTMs, and their structural and functional effects on the heme proteins. This progress helps us to understand how PTMs fine-tune the structure and function of heme proteins, and provides us with new approaches for design of artificial heme proteins by using the positive PTMs. Moreover, we may regulate the negative PTMs by rational design of inhibitors toward our desired goals.

2. Heme-protein cross-links

2.1. Cross-link with heme side chains

As reviewed the progress in four decades from 1974 to 2015, a broad diversity of cross-links have been discovered between amino acids and the heme side chains, such as Cys/SeCys/Met/His/Trp/Tyr-heme vinyl groups and Glu/Asp-heme methyl group, with bond type ranging from C-S, C-Se, C-N, C-C to C-O (Fig. 1) [15]. This section

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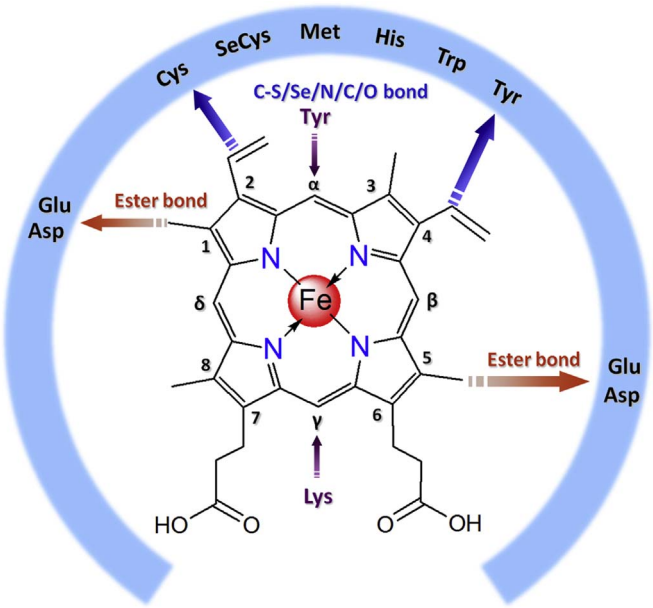

Fig. 1. The broad diversity of heme-protein cross-links. Reprinted with minor modification with permission from Ref. [15]. Copyright 2015 Elsevier.

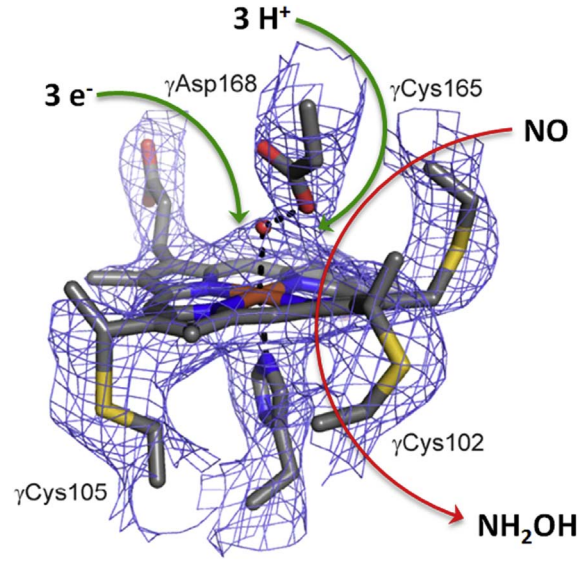

Fig. 2. X-ray crystal structure of heme-γI in the γ-subunit of hydrazine synthase, showing three heme-Cys covalent links, as well as the reaction proposed to be catalyzed in the heme center. Reprinted with minor modification with permission from Ref. [21]. Copyright 2015 Macmillan publishers.

focuses on the most recent progress.

2.1.1. Cys-heme

A common heme-protein cross-link is the thioether bond in *c*-type cytochromes. In most cases, two thioether bonds are formed between the heme vinyl groups and the cysteine sulfurs of a classic CXXCH heme-binding motif [16]. The attachment of heme to an (A/F)XXCH motif with a single thioether bond was also discovered [17,18], suggesting that the two thioether bonds could be formed individually. This was also evidenced in Cyt *c* variants with a single thioether bond by construction of a XXXCH or CXXXH heme-binding motif [19,20]. Dietl et al. resolved an X-ray structure of hydrazine synthase (HZS) multiprotein complex [21]. The electron density map showed that, in the γ-subunit in addition to two common *c*-type thioether bonds (Cys102 and Cys105), the sulfur atom of Cys165 forms a unique third thioether bond with the heme (γI) C1 porphyrin methyl group (Fig. 2), which is believed to be capable of modulating the heme chemistry. Unlike most Cyts *c* with a Met/His six-coordination, the heme-γI is coordinated by H_2O/His with a distal Asp forming a H-bond network, which may assist in proton transfer. As proposed, the heme-γI active site catalyzes the reduction of nitric oxide to hydroxylamine ($NO + 3H^+ + 3e^- \rightarrow NH_2OH$, Fig. 2), by further obtaining three electrons, likely from the triheme Cyt *c* kuste2854 [22]. NH_2OH then diffuses to the heme active site in the α-subunit, where it further reacts with NH_3, producing the final product hydrazine ($NH_2OH + NH_3 \rightarrow N_2H_4 + H_2O$).

2.1.2. Tyr-heme

The Tyr-heme cross-link with a C-O bond is a new PTM of heme proteins, which was discovered by us in F43Y sperm whale Mb mutant between the Tyr hydroxyl group and the heme 4-vinyl group [23]. To tune the formation of Tyr-heme cross-link by using H-bond interactions, we introduced an additional histidine (L29H) in the heme distal site of F43Y Mb, which yields two distinct forms of the double mutant, L29H/F43Y Mb, without and with the Tyr-heme cross-link (Fig. 3A and B, respectively) [24]. A direct comparative study was then made to reveal the structural and functional consequences of formation of Tyr-heme cross-link in the same protein scaffold. The results showed that the Tyr-heme cross-link regulates the H-bond network in the heme distal site, which fine-tunes both the binding of ligands (such as imidazole and fluoride ions) and the protein reactivity, with the cross-linked form more reactive toward activation of H_2O_2. UV-Vis and electron paramagnetic resonance (EPR) studies provided further insights into the formation of Tyr-heme cross-link upon DTT-induced reduction in presence of O_2. The process presumably involves receiving electrons from DTT, the activation of O_2 and formation of catalytic intermediates such as Compound I (oxoferryl heme π-cation radical) and Compound II (oxoferryl heme) (Scheme 1).

With a non-dissociable heme group due to the Tyr-heme cross-link, F43Y Mb offers an ideal protein scaffold for design of functional heme proteins. Recently, we have designed several functionally active, artificial Dye-decolorizing peroxidases (DyPs) by further introduction of Tyr/Trp to the secondary sphere of the heme center in F43Y Mb, including F43Y/I107Y Mb, F43Y/F138 W Mb and F43Y/I107Y/F138W Mb [25]. In particular, the double mutant F43Y/F138 W Mb exhibits an overall catalytic efficiency (k_{cat}/K_m) of 110 670 $M^{-1}\cdot s^{-1}$ toward decolorization of reactive blue 19 (RB19) (Fig. 4), which is ~144-fold and ~20-fold that of WT Mb and F43Y Mb, respectively, and is ~4.3-fold that of native DyP from *Vibrio cholerae* [26], suggesting potential applications of the artificial DyP in parallel with the native enzymes.

2.1.3. Asp/Glu-heme

A striking structural feature of mammalian peroxidases, such as lactoperoxidase (LPO), myeloperoxidase (MPO), eosinophil peroxidase (EPO) and thyroid peroxidase (TPO), is the heme-protein cross-links *via* two ester bonds formed between two heme methyl groups and the carboxyl groups of Asp/Glu [27]. Recently, Singh and co-workers reported an X-ray structure of bovine LPO with a partially covalently linked heme group [28]. The structure at 1.98 Å resolution revealed two distinct conformations for the side chain of Glu258, each with a 0.5 occupancy (Fig. 5A). In the absence of an ester bond between Glu258 and the heme 1-metal group, Glu258 interacts with distal residues, Gln105 and His109, as well as distal water molecules, which may block the binding of substrates to the heme site. On the other hand, the formation of the ester bond stabilizes the heme position and improves the heme reactivity (Fig. 5B). This was supported by a mutagenesis study of Glu258 to Gln258 that results in the loss of the catalytic activity [29].

Peroxidases homologous to mammalian counterparts are also found in bacteria [30]. For example, Obinger and co-workers reported the occurrence of a stable LPO-like peroxidase from cyanobacterium *Lyngbya* sp. PCC 8106 (LspPOX) with two heme to protein ester linkages

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