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Review

Structure and function of atypically coordinated enzymatic mononuclear non-heme-Fe(II) centers

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ABSTRACT

Mononuclear, non-heme-Fe(II) centers are key structures in O_2 metabolism and catalyze an impressive variety of enzymatic reactions. While most are bound via two histidines and a carboxylate, some show a different organization. A short overview of atypically coordinated O_2 dependent mononuclear-non-heme-Fe(II) centers is presented here Enzymes with 2-His, 3-His, 3-His-carboxylate and 4-His bound Fe(II) centers are discussed with a focus on their reactivity, metal ion promiscuity and

Abbreviations: 1,3-bis(2-pyridylimino)isoindoline, ind; 2OH-1,3-Ph_2PD, 2-hydroxy-1,3-diphenylpropanedione; 6-Ph_2TPA, N,N-bis[(6-phenyl-2-pyridyl)methyl]-N-[(2-pyridyl)-methyl]amine; α-KG, α-ketoglutarate; acac, acetylacetone (2,4-pentanedione); ADO, cysteamine dioxygenase; AO, apocarotenoid 15,15′-oxygenase; ARD, aci-reductone dioxygenase; BsQDO, quercetin 2,3-dioxygenase from *Bacillus subtilis*; CarOs, carotenoid oxygenases; CD, circular dichroism; CDO, cysteine dioxygenase; CGDO, 5-chloro-gentisate 1,2-dioxygenase; CS2, clavaminate synthase; DFT, density functional theory; Dke1, diketone dioxygenase; EPR, electron paramagnetic resonance; EXAFS, extended X-ray absorption fine structure spectroscopy; fla, flavonolate; GDO, gentisate 1,2-dioxygenase; HADO, 3-hydroxyanthranilate 3,4-dioxygenase; HGDO, homogentisate 1,2-dioxygenase; HNDO, hydroxy-2-naphthoate dioxygenase; MCD, magnetic circular dichroism; MNHEs, mononuclear non-heme-Fe(II) dependent enzymes; NRP, nonribosomal peptide; OTf-, trifluormethanesulfonate; PDB, protein data bank; QDO, quercetin 2,3-dioxygenase; SDO, salicylate 1,2-dioxygenase; TauD, taurine hydroxylase; XAS, X-ray absorption spectroscopy.

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[1] This review focuses on mononuclear non-heme iron enzymes that utilize O_2 as a co-substrate. Furthermore, it is restricted to enzymes that use Fe(II) in the resting form of the catalytically competent enzyme. Consequently, lipoxygenases, which show a distinct metal center geometry and depend on the activation of the primary Fe(II) center to Fe(III), which is then the catalytically competent – substrate activating – form of the active site, are not discussed.

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recent progress in the elucidation of their enzymatic mechanisms. Observations concerning these and classically coordinated Fe(II) centers are used to understand the impact of the metal binding motif on catalysis.

1. Introduction—mononuclear non-heme-Fe(II) and O_2 dependent enzymes (MNHEs)[1]

MNHEs are key-players in O_2 metabolism, on which aerobic life depends. The catalytic diversity of MNHEs, which comprises chemically challenging reactions such as hydroxylation, desaturation, C—C bond breakage and ring closure, parallels and complements the versatility of the heme containing P450 enzymes [1,2]. MNHEs generally bind and activate O_2 directly at the Fe(II) center and the resulting iron oxygen intermediates react with the organic substrate(s) to form the products. As the one-electron reduction of O_2 at the iron center is thermodynamically unfavorable [3], additional electron sources are generally required to promote dioxygen activation [4]. MNHEs can be grouped according to the respective electron-source into 'self sufficient' cofactor independent enzymes and O_2 activating enzymes that depend on cofactors such as pterin, α-ketoglutarate (α-KG), ascorbate or an electron providing Rieske cluster [1,2,5]. Examples of typical reactions that are catalyzed by MNHEs are summarized in Fig. 1.

MNHEs generally share a common metal binding motif, termed the 2-His-1-carboxylate 'facial' triad, where two histidine and one carboxylate-containing side chain are arranged at one face of an octahedron [6–8]. The other three coordination positions provide sites for O_2 and the organic substrate(s) or – in the enzyme's resting state – water ligands. This general arrangement is believed to allow for an efficient coupling of dioxygen activation and substrate oxidation with water ligands protecting the metal center from auto-oxidation and uncoupled cofactor oxidation (Fig. 2 A). Only when all required co-substrates (B) and substrates are bound to the active site is a coordination site vacated, due to steric interactions and/or donor-effects of the chelating (co)substrate, (C) and O_2 can bind to Fe(II) (D) [9,2].

2. Atypically coordinated mononuclear non-heme-Fe(II) centers

Rather recently, a handful of O_2 dependent MNHEs with distinct reactivities and metal binding motifs have been reported, raising the questions of why most MNHEs have the facial triad and what function is associated with the unconventional metal centers. A deeper understanding of the structural role of the metal center in MNHEs is important to fully exploit the synthetic potential of the MNHE catalytic center in the design of new functions. 'Atypical' non-heme-Fe(II) binding sites coordinate the metal center by (i) two histidine-, (ii) three histidine-, (iii) three histidine- and one carboxylate- and (iv) four histidine-side chains. Interestingly, with the exception of the 4-His binding motif, the atypically coordinated non-heme-Fe(II) centers are generally found in proteins that

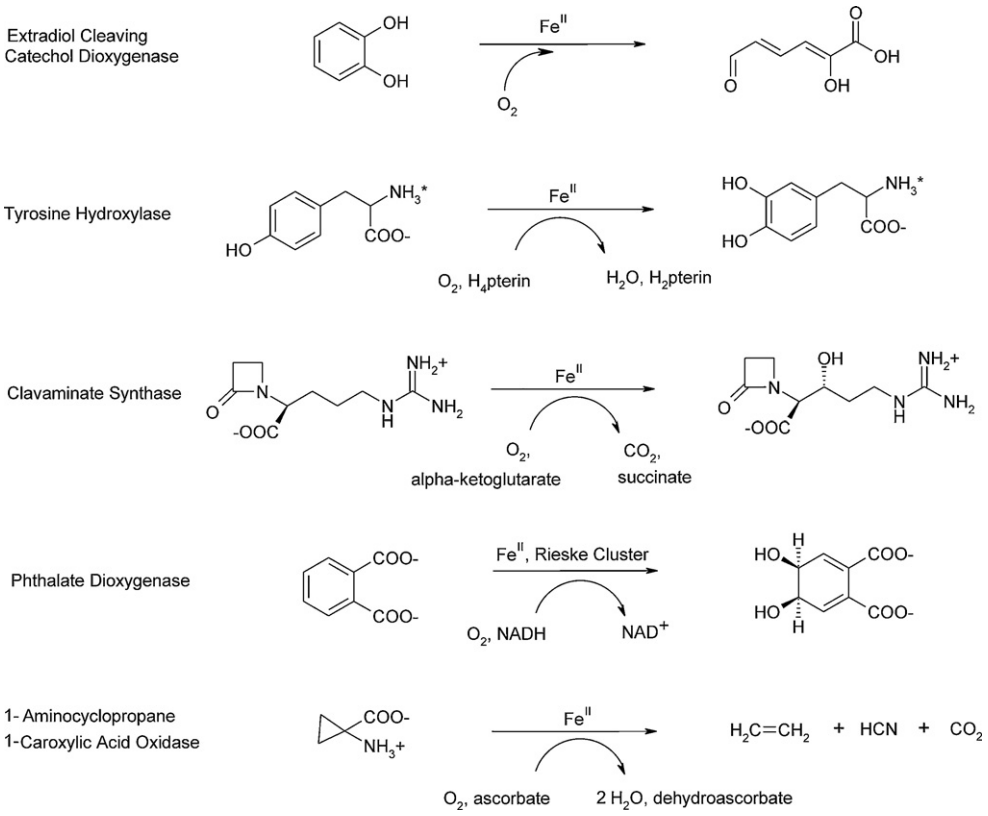

Fig. 1. Prototypical reactions of MNHEs that show the 2-His-1-carboxylate 'facial triad' Fe(II)-binding motif.