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Human copper-dependent amine oxidases ☆

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ABSTRACT

Copper amine oxidases (CAOs) are a class of enzymes that contain Cu^{2+} and a tyrosine-derived quinone cofactor, catalyze the conversion of a primary amine functional group to an aldehyde, and generate hydrogen peroxide and ammonia as byproducts. These enzymes can be classified into two non-homologous families: 2,4,5-trihydroxyphenylalanine quinone (TPQ)-dependent CAOs and the lysine tyrosylquinone (LTQ)-dependent lysyl oxidase (LOX) family of proteins. In this review, we will focus on recent developments in the field of research concerning human CAOs and the LOX family of proteins. The aberrant expression of these enzymes is linked to inflammation, fibrosis, tumor metastasis/invasion and other diseases. Consequently, there is a critical need to understand the functions of these proteins at the molecular level, so that strategies targeting these enzymes can be developed to combat human diseases.

Introduction

Copper amine oxidases (CAOs)[1] are copper- and quinone-dependent enzymes that catalyze the oxidative deamination of primary amine functional groups to aldehydes, concomitantly producing hydrogen peroxide and ammonia. Currently, they are grouped into two nonhomologous subgroups based on the nature of their organic cofactors, namely 2,4,5-trihydroxyphenylalanine quinone (TPQ)-dependent CAOs and the lysine tyrosylquinone (LTQ)-dependent lysyl oxidase (LOX) family of proteins [1]. A number of reviews of CAOs and LOXs are available [1–11], including an excellent recent review by Klema and Wilmot that focuses on structural biology studies of the mechanisms of TPQ biogenesis and catalysis of amine oxidation in the TPQ-containing bacterial and yeast CAOs [12]. In the present review, we will first briefly summarize the current understandings of the mechanisms of (1) TPQ and LTQ biogenesis and (2) amine oxidation by CAOs and LOX. We will also discuss their commonly used *in vitro* inhibitors. We will then highlight recent research developments concerning human CAOs and the human LOX family of proteins, with an emphasis on their proposed roles in disease and health defects.

Tyrosine-derived quinone cofactors: TPQ and LTQ

TPQ and LTQ (Fig. 1) were discovered by Klinman and coworkers as the respective organic cofactors of a CAO isolated from bovine plasma and a LOX isolated from bovine calf aorta [13,14]. Both cofactors are post-translationally derived from a conserved active-site tyrosine residue via an autocatalytic mechanism requiring only Cu^{2+} and O_2 [15,16]. Dopaquinone (DPQ) is proposed to be the common intermediate during the biogenesis of TPQ and LTQ, where the 1,4-addition of either water or the ε-amino side chain of a peptidyl lysine residue to DPQ yields TPQ or LTQ, respectively [13,14] (Fig. 2). A careful inspection of the reaction product of TPQ biogenesis in the presence of $H_2{}^{18}O$ and $^{18}O_2$ by resonance Raman spectroscopy revealed that the C2 oxygen of TPQ is from solvent water, rather than O_2 [17]. In the same study, substantial electron delocalization between the C2 and C4 oxygens of the TPQ cofactor was observed, whereas the C5=O bond had more carbonyl character. These results support a solution study demonstrating that the delocalization directs the addition of substrate amine at the C5 carbonyl group [18].

X-ray snapshot analysis of TPQ biogenesis revealed that the precursor tyrosine and the biogenesis intermediates (i.e. DPQ and the trihydroxybenzene form, i.e. TPQ_{red}) are all ligated to Cu^{2+}

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[1] *Abbreviations used:* CAOs, copper amine oxidases; TPQ, 2,4,5-trihydroxyphenylalanine quinone; LTQ, lysine tyrosylquinone; LOX, lysyl oxidase; DPQ, dopaquinone; SSAOs, semicarbazide-sensitive amine oxidases; maoA and maoB, monoamine oxidases A and B; BAPN, β-aminopropionitrile; SRCR, scavenger receptor cysteine-rich; DAO, diamine oxidase; KAO, kidney amine oxidase; ABP, amiloride-binding protein; RAO, retina-specific amine oxidase; RMSD, root mean square deviation; VAP-1, vascular adhesion protein-1; PAO, plasma amine oxidase; CHO, Chinese hamster ovary; COPD, chronic obstructive pulmonary disease; ERAD, endoplasmic reticulum-associated protein degradation; ECM, extracellular matrix; XFS, exfoliation syndrome; ESTs, expressed sequence tags; POP, pelvic organ prolapse; ERK, extracellular signal-regulated kinase; MMP2, matrix metalloproteinase 2; AP1, activator protein 1; HNSCC, head and neck squamous cell carcinoma.

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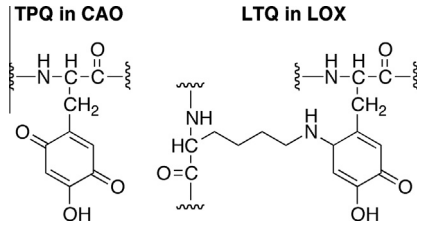

Fig. 1. Structures of TPQ and LTQ, tyrosine-derived quinone cofactors of human CAOs. TPQ (*left*) is derived from a conserved Tyr residue in CAOs, while LTQ (*right*) is derived from conserved Tyr and Lys residues in LOX. From [13,14].

(i.e. "on-copper" forms) at their O4 oxygen atoms [19]. In the last O_2-oxidation step of TPQ_{red} to TPQ, the TPQ ring finally moves away from the Cu^{2+} binding site and becomes trapped in a hydrophobic wedge-like cavity in the active site; this is the "off-copper" conformation (Fig. 3) (described in greater detail under ***Reaction Mechanism***). The conformational change of TPQ is critical for optimal catalytic activity of CAOs, since the on-copper form of TPQ is unable to interact with substrate amines [7,20,21]. The factor that drives TPQ to move off Cu^{2+} in the final step of biogenesis remains to be elucidated.

In contrast to TPQ, the details of the LTQ biogenesis mechanism (Fig. 2) have not been explored, mainly due to the unavailability of diffracting crystals suitable for X-ray crystallography. However, to gain some insight in the intermediacy of DPQ in the biogenesis of TPQ and LTQ, a lysine residue was incorporated into the active site of a bacterial CAO by site-directed mutagenesis, replacing the conserved Asp residue located at the far end of the wedge [22]. In this mutant, an LTQ-like quinone was produced instead of TPQ, where the covalent bond between the lysine side chain and DPQ was confirmed by X-ray crystallography (Fig. 4). These results not only support the hypothesized common intermediacy of DPQ in the biogenesis of TPQ and LTQ [7,23], but also suggest that at room temperature the DPQ intermediate has sufficient motional flexibility to swing out of the Cu^{2+} site and interact with the ε-amino group of the lysine side chain in the wedge (Fig. 4).

Reaction mechanism of CAOs and LOX in amine oxidation

The reaction mechanism of CAOs in the oxidation of primary amines follows a classical ping-pong mechanism involving covalent intermediates formed between TPQ and amines, as well as oxidoreduction reactions of the TPQ cofactor (Fig. 5) [7,8,12]. A conserved Asp residue acts as an active site base to remove an α-proton from the first covalent intermediate between TPQ and the substrate amine (i.e. a substrate Schiff base), and also serves as a proton sink to regulate the protonation state of the substrate and the TPQ-derived reaction intermediates, which are essential for optimal catalytic activity [24–26] (Fig. 6). The protonation state

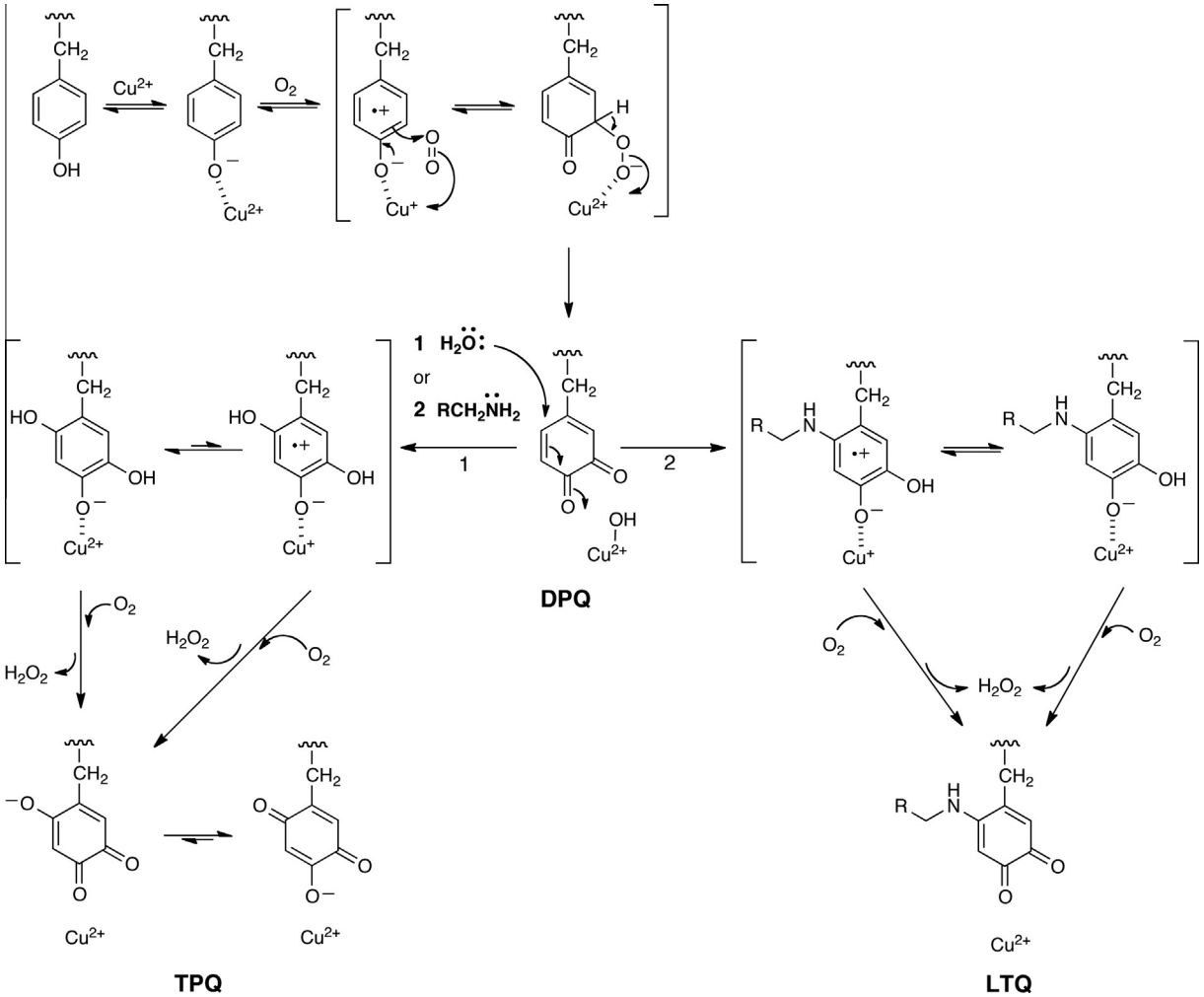

Fig. 2. DPQ as a common intermediate in the biogenesis of TPQ and LTQ. The proposed mechanisms for the biogenesis of the TPQ and LTQ cofactors share a dopaquinone (DPQ) intermediate. The 1,4-addition of either water (*Pathway 1*) or the ε-amino side chain of a peptidyl lysine residue (*Pathway 2*) to DPQ yields TPQ or LTQ, respectively. RCH_2NH_2 represents the side chain of a peptidyl lysine residue ($-CH_2CH_2CH_2CH_2NH_2$) within the polypeptide of a LOX family member. Adapted from [13,14].