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Review

Oxidative modification of free-standing amino acids by Fe(II)/αKG-dependent oxygenases

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ABSTRACT

Fe(II)/α-ketoglutarate (αKG)-dependent oxygenases catalyze the oxidative modification of various molecules, from DNA, RNA, and proteins to primary and secondary metabolites. They also catalyze a variety of biochemical reactions, including hydroxylation, halogenation, desaturation, epoxidation, cyclization, peroxidation, epimerization, and rearrangement. Given the versatile catalytic capability of such oxygenases, numerous studies have been conducted to characterize their functions and elucidate their structure–function relationships over the past few decades. Amino acids, particularly nonproteinogenic amino acids, are considered as important building blocks for chemical synthesis and components for natural product biosynthesis. In addition, the Fe(II)/αKG-dependent oxygenase superfamily includes important enzymes for generating amino acid derivatives, as they efficiently modify various free-standing amino acids. The recent discovery of new Fe(II)/αKG-dependent oxygenases and the repurposing of known enzymes in this superfamily have promoted the generation of useful amino acid derivatives. Therefore, this study will focus on the recent progress achieved from 2019 to 2022 to provide a clear view of the mechanism by which these enzymes have expanded the repertoire of free amino acid oxidative modifications.

1. Introduction

Fe(II)- and α-ketoglutarate (αKG)-dependent oxygenases are widely distributed in nature, including microorganisms, plants, and vertebrates. During the past few decades, many studies have intensively investigated the mechanisms and structure–function relationships of Fe(II)/αKG-dependent oxygenases. These efforts have revealed a generic mechanism and common double-stranded β-helix fold shared by the members of this superfamily [1,2,34,41,49,53,57,81,83]. Fe(II)/αKG-dependent oxygenases catalyze the oxidative modification of primary and secondary metabolites, using O_2 with Fe(II) as the cofactor and αKG as the cosubstrate [40,43,59]. The oxidative decarboxylation of αKG to succinate generates a highly reactive Fe(IV)-oxo species, which selectively oxidizes inactivated C–H bonds and leads to a wide array of biochemical reactions, including hydroxylation, halogenation, desaturation, epoxidation, cyclization, peroxidation, epimerization, and rearrangement [10,17,22,25,33,56,63,65,68,71,85,92,97].

Given their association with numerous biological processes, Fe(II)/αKG-dependent oxygenases play an important role in nature [36]. Many Fe(II)/αKG-dependent oxygenases account for the modification of chromatin, DNA, and proteins, as well as the demethylation/hydroxylation of RNA [5,47,48,52,57]. Thus, such oxygenases have been reviewed recently [36]. Furthermore, given their versatile catalytic roles and synthetic capabilities, Fe(II)/αKG-dependent oxygenases can oxidize primary metabolites, such as amino acids, and tailor various biologically important natural products, including alkaloids and meroterpenoids [15,44,56,63,66,78,90,92]. The structure–function relationship of Fe(II)/αKG-dependent oxygenases in the biosynthesis of natural products, particularly meroterpenoids, have been summarized in excellent reviews [7,26,28,36,54,64,84,91,98,104]. In addition, the characterization and engineering of halogenases have been summarized in reviews published in 2022 [74,96]. Thus, this study will focus on Fe(II)/αKG-dependent oxygenases that are responsible for amino acid modifications.

Amino acid derivatives are considered as important nutritional supplements, pharmaceutical intermediates, and building blocks for organic synthesis and natural product biosynthesis [60,88,101]. Given their versatile applications, an increasing number of Fe(II)/αKG-dependent oxygenases have been characterized for amino acid modifications. They oxidize carrier protein-bound and free-standing amino acids during natural product biosynthesis. For example, KtzO and KtzP cannot accept free-standing L-Glu-during kutzneride biosynthesis. Thus, they hydroxylate L-Glu-bound to a peptidyl carrier protein and generate L-*threo*- and L-*erythro*-hydroxyglutamic acids, respectively [87]. By contrast, some Fe(II)/αKG-dependent hydroxylases accept free amino acids as substrates, such as the proline hydroxylase P3H/P4H [30,61,62], the

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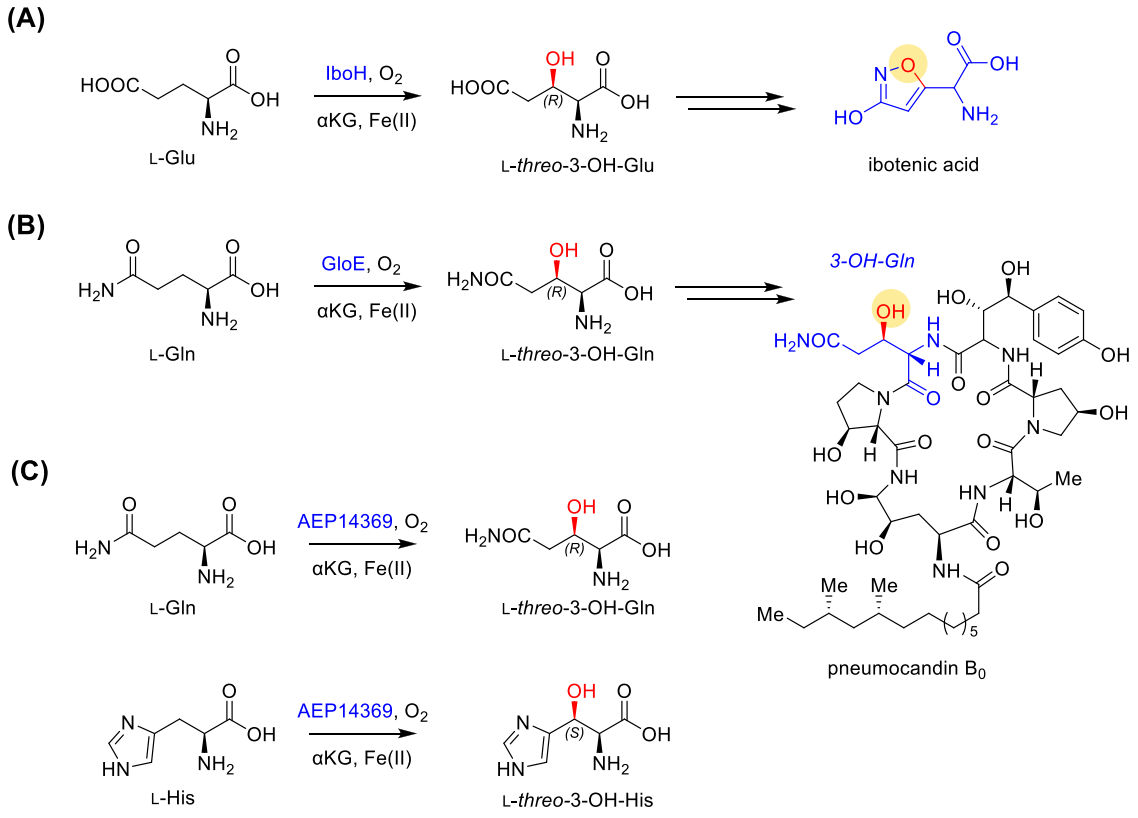

Fig. 1. *β*-Hydroxylation of free-standing amino acids by (**A**) IboH, (**B**) GloE, and (**C**) AEP14369.

isoleucine 4-hydroxylase IDO [37,42,70,99], the leucine 5-hydroxylases LdoA and GriE [38,51,103], the lysine 3/4-hydroxylases KDO and K3H/K4H [8,32], the arginine 3-hydroxylase VioC [21,35,100], and the glutamine 3-hydroxylase AsnO [86]. These *α*KG-dependent amino acid hydroxylases have been described in previous reviews [26,39,53,74,75]. Therefore, we will primarily discuss the recent progress achieved from 2019 to 2022. Apart from summarizing the new Fe(II)/*α*KG-dependent enzymes that were recently discovered and characterized for the oxidative modification of free-standing amino acids, we will also focus on reactions involving known repurposed enzymes, which facilitate the generation of useful amino acid derivatives.

2. Discovery of new Fe(II)/*α*KG-dependent oxygenases to expand the repertoire of amino acid oxidative modifications

2.1. Hydroxylation of amino acids by Fe(II)/αKG-dependent oxygenases

2.1.1. β-Hydroxylation

β-Hydroxy (*β*-OH or 3-OH) amino acids, including *β*-fluoro amino acids and *β*-lactams, are important precursors for pharmaceuticals and building blocks for organic synthesis [50,73]. In addition, *β*-OH amino acids are found in biologically active natural products, such as *β*-OH-Glu-in kutznerides [87] and *β*-OH-Arg-in viomycin [100]. Fe(II)/*α*KG-dependent oxygenases are also important, as they not only modify amino acids tethered to a carrier protein, such as the generation of *β*-OH-Glu-bound to the peptidyl carrier protein by KtzO and KtzP during kutznerside biosynthesis [87], but also hydroxylate free-standing amino acids, such as L-Arg-by VioC [100] and L-Lys-by KDO1 [8]. However, until the characterization of IboH, which is the first reported Fe(II)/*α*KG-dependent oxygenase for the hydroxylation of free L-Glu, no Fe(II)/*α*KG-dependent oxygenase that could catalyze the *β*-hydroxylation of free-standing L-Glu-had been identified [69] (Fig. 1A). IboH is encoded in the ibotenic acid biosynthetic gene cluster from *Amanita muscaria*. It accepts free L-Glu-to generate the product L-*threo*-3-OH-Glu, which initiates the biosynthesis of ibotenic acid in fly agaric. Moreover, IboH has a strict substrate preference, as L-Gln, which has a similar structure to L-Glu, was not accepted [69].

β-OH-Gln-was discovered in the nonribosomal peptide pneumocandin B_0 [46]. In the biosynthetic gene cluster of pneumocandin B_0, an Fe(II)/*α*KG-dependent oxygenase, GloE, was characterized as the *β*-hydroxylase that generates L-*threo*-*β*-OH-Gln-from free-standing L-Gln (Fig. 1B) [79]. In addition to GloE, AEP14369 from *Sulfobacillus thermotolerans* Y0017 accepted L-Gln [31]. AEP14369 was characterized as an Fe(II)/*α*KG-dependent *β*-hydroxylase that selectively generates L-*threo*-*β*-OH-Gln-and L-*threo*-*β*-OH-His-from L-Gln-and L-His, respectively (Fig. 1C). *β*-OH-L-His-is present in many natural products, including nikkomycin [18], siderophores [13,29], and bleomycin [89,95]. During nikkomycin biosynthesis, the heme- and NADPH-dependent protein NikQ catalyzes the *β*-hydroxylation of L-His-bound to a carrier protein domain [18]. The generation of *β*-OH-His-in siderophores [77] and glidomides [19] is performed by Fe(II)/*α*KG-dependent *β*-hydroxylases that use thiolation domain-bound L-His-as a substrate. Notably, no Fe(II)/*α*KG-dependent enzyme that accepts free-standing L-Gln-and L-His-had been reported until the discovery of GloE and AEP14369, which expanded the reaction repertoire of Fe(II)/*α*KG-dependent *β*-hydroxylases.

2.1.2. γ-Hydroxylation

γ-Hydroxy (*γ*-OH or 4-OH) amino acids are biologically and pharmacologically important, as they are widely used as nutritional supplements (*e.g.*, *trans*-4-OH-L-Pro), antidiabetic drugs (*e.g.*, 4-OH-L-Ile, 4-OH-L-norVal, and 4-OH-L-Pip), and chiral building blocks for organic synthesis [60,101]. Furthermore, *γ*-OH-amino acids are important building blocks for natural products. Newly discovered Fe(II)/*α*KG-dependent *γ*-hydroxylases have been characterized for the generation of 4-OH-L-Lys-in glidobactin [3], 4-OH-L-Gln-in gramillin A [79], and 4-OH-L-Cit in GE81112A [105] (Fig. 2).

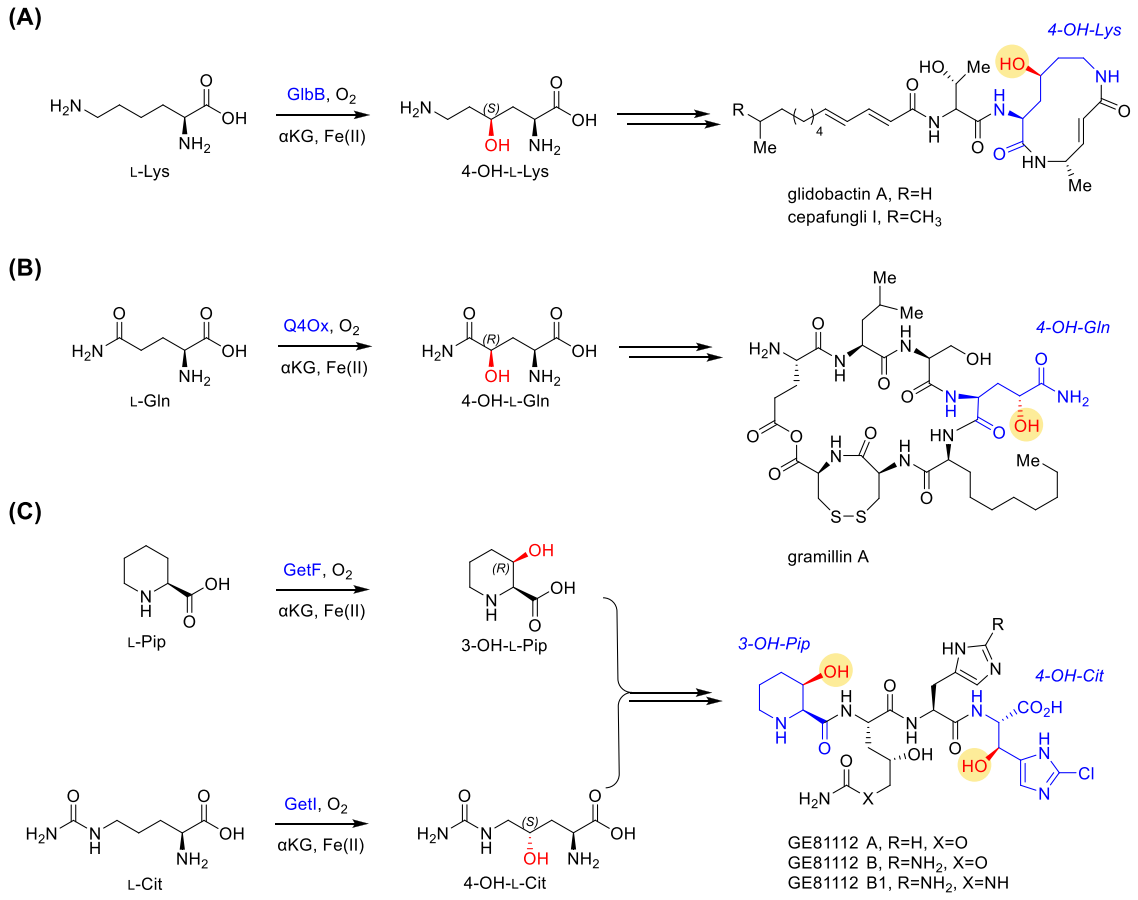

Fig. 2. γ-Hydroxylation of free-standing amino acids by (**A**) GlbB, (**B**) Q4Ox, and (**C**) GetI.

Based on previous reports, L-Lys-hydroxylases such as KDO2, KDO3, and K4H produce (4*R*)−4-OH-L-Lys [8,32]. In contrast to these enzymes, an Fe(II)/αKG-dependent oxygenase, GlbB, was found to selectively generate (4*S*)−4-OH-L-Lys-during glidobactin biosynthesis (Fig. 2A) [3]. Biochemical characterization revealed that GlbB not only catalyzes the efficient γ-hydroxylation of free-standing L-Lys-with complete regio- and diastereoselectivity, but also hydroxylates aliphatic amino acids (L-Leu-and L-Met) with moderate total turnover numbers [3]. Notably, Fe(II)/αKG-dependent hydroxylases selectively act on aliphatic amino acids (*e.g.,* IDO) [37,42,70] or polar amino acids (*e.g.,* VioC) [21,35,100]. Therefore, GlbB is the first enzyme in this family that accepts both aliphatic and polar amino acids. Furthermore, the chemoenzymatic synthesis of cepafungin I, which is a potent inhibitor of the 20S proteasome core, was achieved through the 4-hydroxylation of L-Lys-with GlbB [3].

4-OH-L-Gln-was detected in nonribosomal peptide gramillin A, whose biosynthetic gene cluster contains the gene encoding the Fe(II)/αKG-dependent oxygenase Q4Ox [79]. Biochemical characterizations revealed that Q4Ox produced (4*R*)−4-OH-L-Gln-from free-standing L-Gln-with complete diastereoselectivity (Fig. 2B), thereby providing a new enzyme for the preparation of useful glutamine derivatives.

GE81112s, which inhibit prokaryotic translation initiation, are nonribosomal tetrapeptides that contain several unusual amino acid building blocks, including 3-OH-L-Pip, 4-OH-L-Cit, and β-OH-2-Cl-L-His [12,24]. Two Fe(II)/αKG-dependent oxygenases, GetI and GetF, were identified in the biosynthetic gene cluster of GE81112s [9]. In previous studies, GetF was characterized as an L-Pip β-hydroxylase, and GetI was annotated as a 2-Cl-L-His β-hydroxylase [9,55]. However, a recent study has revealed that GetI accepts L-Cit rather than 2-Cl-L-His-to generate 4-OH-L-Cit [105] (Fig. 2C). Based on a homology model and sequence alignment analysis, the rational mutagenesis of GetI generated a variant that contains four mutations, as compared with a wild-type enzyme. Moreover, the GetI variant converted substrate preference from L-Cit to L-Arg. With the characterization of GetF and GetI, the chemoenzymatic total synthesis of GE81112 B1 and its analogs was completed, which promoted the first structure–activity studies of the antimicrobial activity of GE81112 [105].

2.2. *Cyclization reactions by Fe(II)/αKG-dependent oxygenases using free amino acids*

2.2.1. *Aziridination by TqaL*

Several Fe(II)/αKG-dependent oxygenases that accept free amino acids have been reported; however, most of them such as IboH [69], GloE [3], and AEP14369 [31] perform common hydroxylation reactions. Cyclization reactions catalyzed by enzymes in this superfamily, including CAS, H6H, HygX, LolO, and FfnD [22,25,33,56,71], have been reported. However, no enzyme was found to catalyze the cyclization of single and free-standing amino acids until the discovery of TqaL, which cyclizes L-Val-to an aziridine-containing product during the biosynthesis of 2-aminoisobutyric acid (AIB), an important building block for bioactive natural products [14] (Fig. 3A). In the biosynthetic gene cluster of tryptoquialanine [27], TqaL was identified and characterized as an Fe(II)/αKG-dependent oxygenase [14]. TqaL could initiate the reaction by abstracting the H-3 of L-Val-via Fe(IV)-oxo species, leading to the generation of a C3-radical species. Subsequently, the C–N bond was formed to complete the aziridine-ring closure by either radical transfer or cation generation [14]. In addition, when the deuterated substrate (2*S*,3*S*)-[4,4,4–$^2H_3$]-Val-with a stereogenic center at C3 was used as a mechanistic probe, TqaL generated a diastereomeric pair of aziridines with the retention and inversion of C3 stereoconfiguration [93]. Furthermore, investigations on the stereoselectivity and substrate speci-

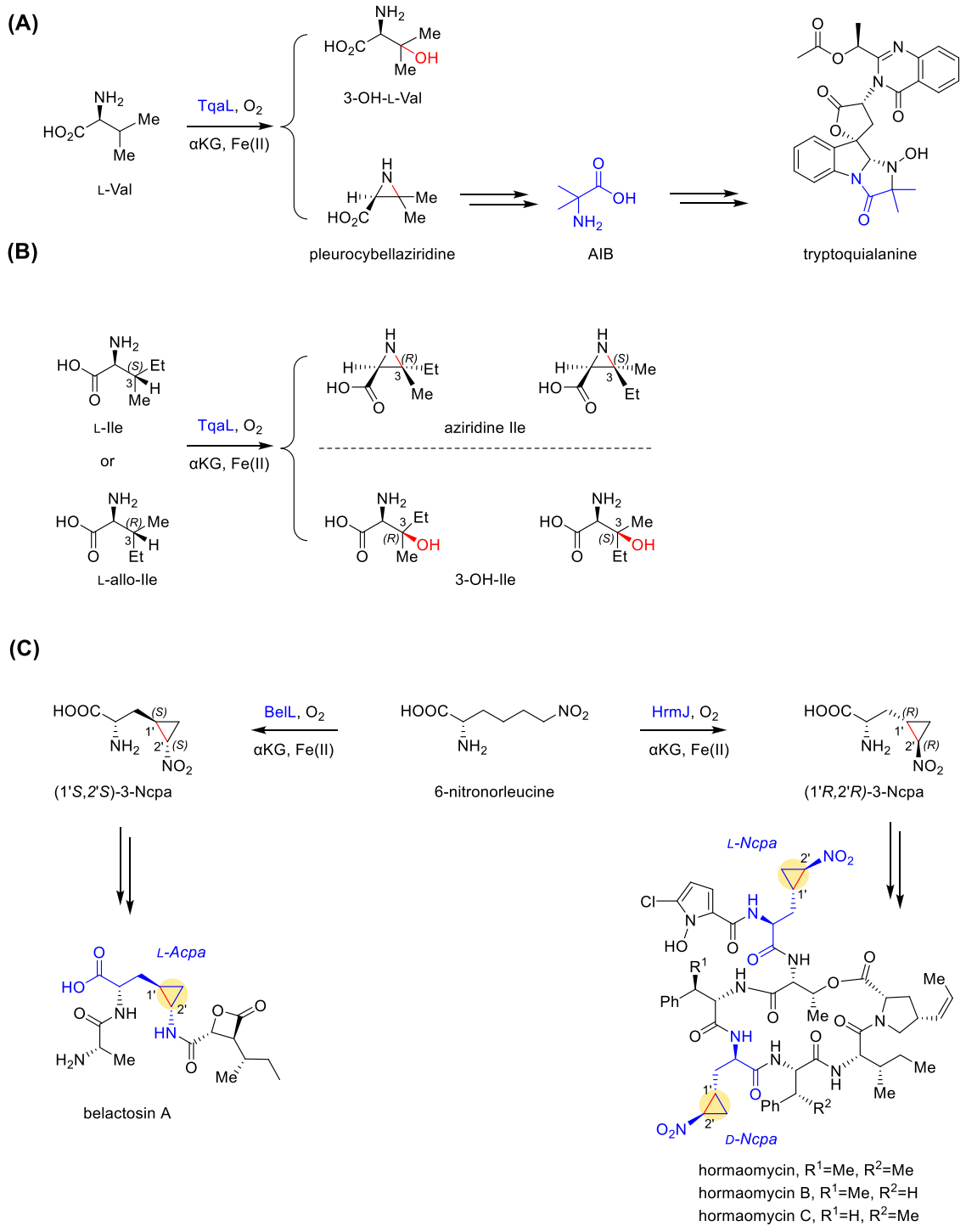

Fig. 3. Cyclization of free-standing amino acids to generate (**A**) aziridine ring from L-Val, (B) Ile-by TqaL, and (**C**) cyclopropane ring by BelL and HrmJ.

ficity of TqaL showed that nonnatural substrates, such as L-Ile-and L-*allo*-Ile, were accepted by TqaL via a stereoconvergent process to generate diastereomeric pairs of aziridine and 3-OH-Ile-products (Fig. 3B), which is consistent with the mixed stereochemical course determined using (2*S*,3*S*)-[4,4,4–$^2H_3$]-Val. Based on mutagenesis studies, the reaction type (aziridination *versus* hydroxylation) and stereochemical outcome of TqaL were regulated by two active site residues (I343 and F345). Furthermore, large-to-small substitution of F345 expanded the substrate scope of TqaL. For example, the F345S variant is highly active toward L-Leu-and L-Met-to generate hydroxy-L-Leu-and L-Met-sulfoxide. Although the detailed mechanism of the aziridine-ring closure requires further investigation, these results have greatly expanded the catalytic repertoire of Fe(II)/*α*KG-dependent oxygenases, thereby indicating that the stereochemical outcomes of the reactions could be rationally controlled by structure-guided mutagenesis.

2.2.2. *Cyclopropanation by BelL and HrmJ*

Natural products with strained three-membered rings, including aziridine and cyclopropane structures, such as aziridine-containing mitomycin and cyclopropane-containing belactosins and hormaomycins, have attracted great interest because of their potent biological activities [4,6,11,94]. In the structure of belactosins and hormaomycins, cyclo-

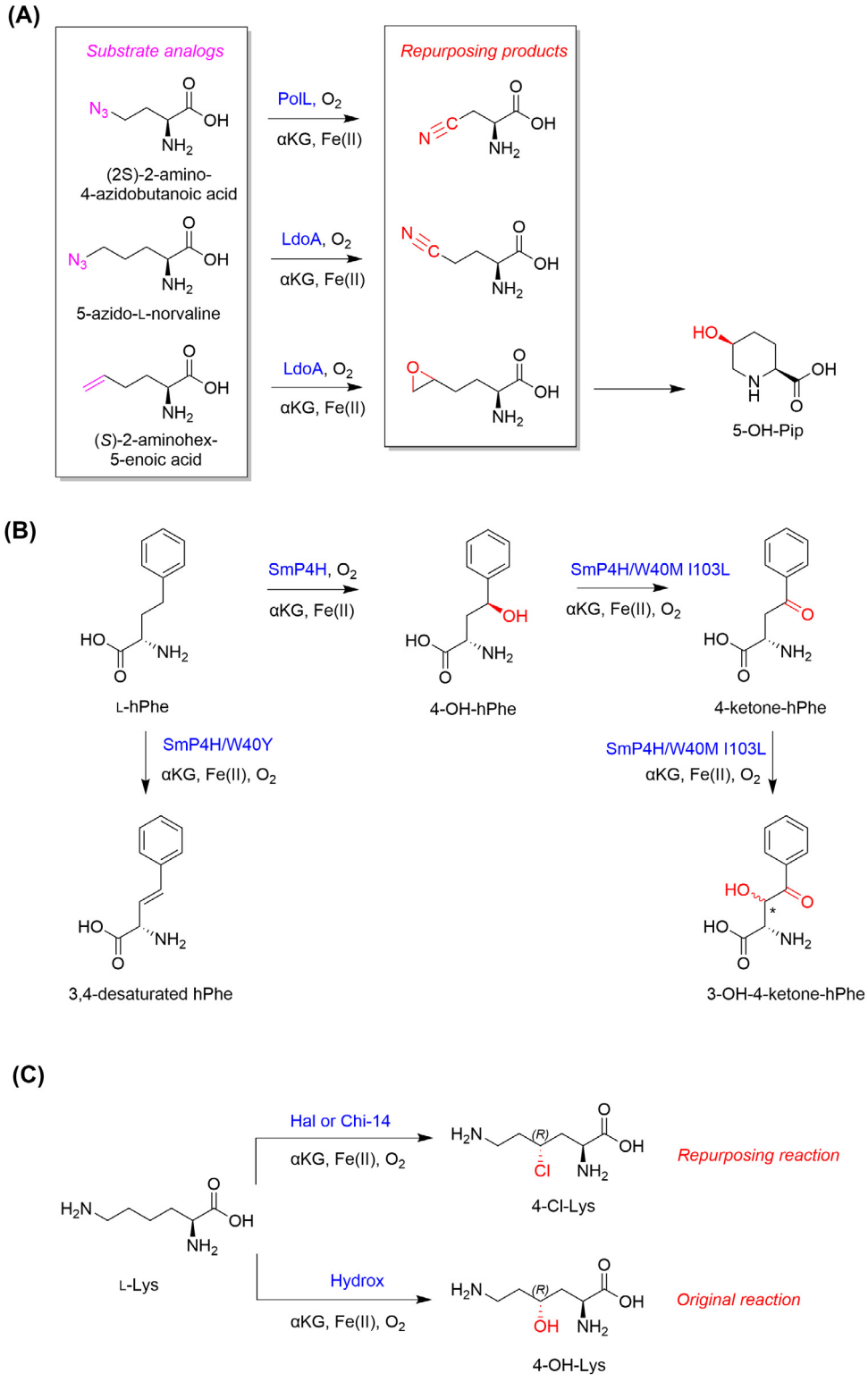

Fig. 4. Repurposing of (**A**) PolL and LdoA for nitrile or epoxide formation and (**B**) SmP4H for L-homophenylalanine oxidation. (**C**) The conversion of L-Lys-hydroxylase to Chi-14 halogenase.

propane rings were found in 3-(2-aminocyclopropyl)alanine (Acpa) and 3-(2-nitrocyclopropyl)alanine (Ncpa) residues, respectively [80,102]. Remarkably, Acpa and Ncpa exhibit opposite stereoconfigurations at C1′ and C2′ in the cyclopropane rings; thus, their biosynthesis has attracted great attention [23,45,72,82]. Two heme oxygenase-like diiron enzymes (BelK and HrmI, 51% identity) and two Fe(II)/αKG-dependent oxygenases (BelL and HrmJ, 49% identity) were discovered by comparing the biosynthetic gene clusters of belactosins and hormaomycins. In addition, *in vitro* and *in vivo* experiments revealed that BelK and HrmI oxidize L-Lys-to 6-nitro-norLeu, which is subsequently accepted by BelL or HrmJ to generate Ncpa with opposite stereoconfigurations at the cyclopropane rings [45,72,82] (Fig. 3C). HrmJ produced (1′*R*,2′*R*)-Ncpa with high stereoselectivity, whereas BelL generated (1′*S*,2′*S*)-Ncp as the major product, which is consistent with the stereochemistry of cyclo-

Table 1
Substrate specificity and quantitative data of summarized enzymes.

	Substrates	Kinetics	TTNs	Refs.
IboH	L-Glu	–	–	[69]
GloE	L-Gln	–	44	[79]
AEP14369	L-Gln	k_{cat} = 43.8 ± 4.1 min^{-1} K_M = 1.17 ± 0.27 mM	–	[31]
	L-His	k_{cat} = 35.1 ± 3.9 min^{-1} K_M = 0.83 ± 0.06 mM	–	
GlbB	L-Lys	k_{cat} = 960 ± 84 min^{-1} K_M = 0.034 ± 0.005 mM	5900	[3]
	L-Leu	k_{cat} = 3.2 ± 0.2 min^{-1} K_M = 2.2 ± 0.4 mM	310	
	L-Met	k_{cat} = 12.0 ± 0.3 min^{-1} K_M = 0.45 ± 0.05 mM	330	
Q4Ox	L-Gln	k_{cat} = 250 ± 3 min^{-1} K_M = 0.99 ± 0.03 mM	4300	[79]
GetI	L-Cit	k_{cat} = 69.0 ± 5.3 min^{-1} K_M = 2.1 ± 0.4 mM	470	[105]
	L-Arg	k_{cat} = 250 ± 3 min^{-1} K_M = 0.99 ± 0.03 mM	20	
TqaL	L-Val	k_{cat} = 22.1 ± 1.0 min^{-1} K_M = 172 ± 25 μM	–	[93]
	L-Ile	k_{cat} = 14.5 ± 0.4 min^{-1} K_M = 665 ± 45 μM	–	
	L-*allo*-Ile	k_{cat} = 0.32 ± 0.03 min^{-1} K_M = 270 ± 73 μM	–	
HrmJ	6-nitronorleucine	–	–	[82]
BelL	6-nitronorleucine	–	–	[45]
PolL	(2*S*)−2-amino-4-azidobutanoic acid	k_{cat} = 4.08 ± 0.74 min^{-1} K_M = 1.49 ± 0.65 mM	150	[20]
LdoA	5-azido-L-norvaline	k_{cat} = 1.90 ± 0.18 min^{-1} K_M = 1.30 ± 0.32 mM	180	
	(*S*)−2-aminohex-5-enoic acid	–	–	[16]
SmP4H (WT)	L-hPhe	k_{cat} = 0.015 ± 0.001 min^{-1} K_M = 1.10 ± 0.24 mM	4	[58]
SmP4H/ W40M I103L	L-hPhe	k_{cat} = 1.680 ± 0.068 min^{-1} K_M = 0.40 ± 0.08 mM	39	
Hydrox	L-Lys	k_{cat} = 22.5 ± 0.5 min^{-1} K_M = 0.34 ± 0.05 mM	136	[74]
Hal	L-Lys	k_{cat} = 10.5 ± 0.4 min^{-1} K_M = 0.12 ± 0.03 mM	410	
Chi-14	L-Lys	k_{cat} = 20.3 ± 0.5 min^{-1} K_M = 0.29 ± 0.03 mM	410	

Note: "–" indicates no data has been reported yet. TTNs: Total turnover numbers.

propane rings found in hormaomycins and belactosins. Investigations of the H abstraction site, which used stereoselectively deuterated 6-nitro-norLeu, revealed that BelL and HrmJ selectively abstract 4-*proS*-H, but they exhibited no or little stereoselectivity for the dehydrogenation at C6 [82]. Although additional investigations are necessary to understand the mechanism by which these enzymes control the stereochemistry, these observations have led to the identification of a novel approach for the stereoselective construction of cyclopropane rings in natural products.

3. Repurposing Fe(II)/αKG-dependent oxygenases for the synthesis of new amino acid derivatives

The discovery and characterization of new members in the Fe(II)/αKG-dependent oxygenase superfamily significantly expanded the catalytic repertoire. Recently, the repurposing of previously characterized enzymes, such as LdoA, PolL, and SmP4H, has emerged as a novel approach for generating new amino acid derivatives [16,20,58] (Fig. 4). LdoA from *Nostoc punctiforme* ACC80786 and PolL from *Streptomyces aureochromogenes* are considered as Fe(II)/αKG-dependent oxygenases that catalyze the hydroxylation of L-Leu-at the C5 position [38] and the dihydroxylation of L-α-amino-δ-carbamoylhydroxyvaleric acid at the C3 and C4 positions [76], respectively. In a recent study, LdoA and PolL were found to catalyze nitrile formation when an azido group was introduced into nonnative substrates [20] (Fig. 4A). Moreover, when an olefin group was installed on the LdoA substrate, the reaction was redirected to asymmetric epoxidation, which led to the generation of 5-OH-Pip [16] (Fig. 4A). SmP4H, a proline 4-hydroxylase from *SinoRhizobium meliloti*, was repurposed as an L-homophenylalanine (hPhe) hydroxylase [58] (Fig. 4B). Furthermore, structure-based rational engineering identified the W40M I103L variant with increased activity to generate further oxidized products, including 4-OH-hPhe, 4-ketone-hPhe, and 3-OH-4-ketone-hPhe (Fig. 4B, Table 1). Notably, with only a single-site mutation, the W40Y variant primarily served as a desaturase [58] (Fig. 4B). These studies revealed the catalytic potential of Fe(II)/αKG-dependent oxygenases in synthetic and industrial applications.

Compared with the wide range of Fe(II)/αKG-dependent hydroxylases, the number of halogenases in this superfamily is limited. Recently, the engineering of an Fe(II)/αKG-dependent lysine hydroxylase into a halogenase was achieved [67] (Fig. 4C). Based on the phylogenetic tree of the BesD family, hydroxylases and halogenases are grouped into separate clades. However, a hydroxylase (Hydrox) was included in the clade of putative halogenases. The Hydrox enzyme shares 71% amino acid sequence identity with a halogenase (Hal). Biochemical characterization revealed that Hydrox and Hal catalyze the hydroxylation and chlorination of L-Lys-at the C4 position, respectively. Hydroxylase–halogenase chimeric enzymes were generated by constructing a DNA shuffling library using these two genes, and halogenation-active variants were screened using a high-throughput *in vivo* fluorescent screen strategy. Finally, a variant (Chi-14) with 14 mutations was identified with comparable activity and higher selectivity to the wild-type halogenase Hal (Fig. 4C and Table 1). Most of the key mutations are located on the two β-sheets lining the αKG binding pocket, except for the criti-

cal residue Gly144 that enables chloride coordination to the Fe(IV)-oxo species, thereby indicating the importance of second-sphere residues for protein engineering, as they further tuned the activity and selectivity of the engineered enzyme [67]. This study promotes the conversion of hydroxylases to halogenases, thereby leading to the expansion of enzymatic halogenation.

4. Conclusions

Recently, an increasing number of Fe(II)/αKG-dependent oxygenases were identified and well-characterized, and reaction repurposing was presented as a useful approach for the generation of important amino acid derivatives. The characterization of new Fe(II)/αKG-dependent oxygenases enriched the toolbox for amino acid hydroxylation and cyclization. However, a number of putative Fe(II)/αKG-dependent oxygenases remain unknown, which need to be characterized. Repurposing the function of known Fe(II)/αKG-dependent oxygenases could be achieved by protein engineering and substrate design. For these newly discovered enzymes, although their functions and substrate scopes were characterized, the detailed mechanism and structure–function relationship need further investigations. This could significantly facilitate the rational protein engineering and design of nonnatural substrates. Furthermore, high-throughput screening and machine learning would assist enzyme engineering and boost the development of Fe(II)/αKG-dependent oxygenases as potential catalysts for chemosynthetic and industrial application.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Given his role as Editorial Board Member, Dr. Ikuro Abe, had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Dr. Wei Zhang.

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