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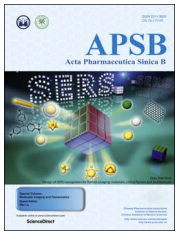

REVIEW

Human carboxylesterases: a comprehensive review

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Abstract Mammalian carboxylesterases (CEs) are key enzymes from the serine hydrolase superfamily. In the human body, two predominant carboxylesterases (CES1 and CES2) have been identified and extensively studied over the past decade. These two enzymes play crucial roles in the metabolism of a wide variety of endogenous esters, ester-containing drugs and environmental toxicants. The key roles of CES in both human health and xenobiotic metabolism arouse great interest in the discovery of potent CES modulators to regulate endobiotic metabolism or to improve the efficacy of ester drugs. This review covers the structural and catalytic features of CES, tissue distributions, biological functions, genetic polymorphisms, substrate specificities and inhibitor properties of CES1 and CES2, as well as the significance and recent progress on the discovery of CES modulators. The information presented here will help pharmacologists explore the relevance of CES to human diseases or to assign the contribution of certain CES in xenobiotic metabolism. It will also facilitate medicinal chemistry efforts to design prodrugs activated by a given CES isoform, or to develop potent and selective modulators of CES for potential biomedical applications.

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1. Introduction

Mammalian carboxylesterases (CES, E.C. 3.1.1.1) are essential members of the serine hydrolase superfamily, which are localized within the lumen of the endoplasmic reticulum in many tissues[1–3]. As their name implies, CES catalyze the ester cleavage of a large number of structurally diverse ester- or amide-containing substrates into the corresponding alcohol and carboxylic acid[1–3]. Actually, CES can hydrolyze ester, thioester, amide, and carbamate linkages in a wide variety of endo- and xenobiotic compounds, thus playing key roles in both endobiotic metabolism, and in activation and/or detoxification of xenobiotics[3–5]. In the human body, three CES have been identified, although human carboxylesterase 1 (CES1) and human carboxylesterase 2 (CES2) are the two extensively studied isoenzymes involved in xenobiotic metabolism[3–8]. Both CES1 and CES2 play crucial roles in the metabolism of various ester xenobiotics including many ester drugs (such as oseltamivir, clopidogrel, irinotecan and capecitabine) and environmental toxicants (such as pyrethroids)[9–13]. These two enzymes are also known to metabolize endogenous esters including cholesteryl esters, triacylglycerols and other endogenous lipids, thus playing vital physiological functions in lipid homeostasis[14–18].

Over the past twenty years, many studies have provided powerful insight into the roles of CES in metabolic diseases and xenobiotic metabolism[14]. The key roles of CES in both endogenous and xenobiotic metabolism have attracted great interest in the discovery of CES modulators to regulate lipid metabolism or to enhance the activity of ester drugs[19–24]. This review covers the structural and catalytic features of CES, tissue distribution, biological functions, substrate specificities and inhibitor profiles of two predominant CES, as well as the significance and recent progress on the discovery of CES modulators. It will be very helpful for pharmacologists to explore the relevance of CES to human diseases or to confirm the contribution of CES in xenobiotic metabolism. In addition, it will assist medicinal chemists in designing ideal prodrugs which can be activated by a given CES isoform in the human body, or to develop more potent inhibitors/inducers of CES.

2. Structural features and catalytic properties of CES

2.1. *Structural features of CES*

CES belong to the *α/β*-hydrolase fold superfamily of proteins. The majority of mammalian carboxylesterases are intracellular proteins found predominantly in the microsomal fraction that encompass the endoplasmic reticulum (ER)[3,25,26]. Microsomal CES from human, rabbit, and mouse carry the HXEL motifs of the KDEL consensus ER retrieval sequence at their C-terminal (such as HIEL and HTEL for CES1 and CES2, respectively), which is essential for the localization of these enzymes to the ER lumen in mammalian cells[26]. Following cleavage of the C-terminal signal peptide, microsomal carboxylesterases can be released from their membrane-associated state, suggesting that these enzymes are not transmembrane proteins but soluble proteins that reside in the ER lumen[9].

The three-dimensional (3D) structures of several mammalian CEs including human carboxylesterase 1 (CES1) have been solved by X-ray crystallography with several ligands[9,25–31]. As depicted in Fig. 1, CES1 is composed by a central catalytic domain, an *αβ* domain, and an adjacent regulatory domain which containing the low-affinity surface ligand-binding Z-site[28,30,31]. The X-ray crystal structure of CES1 demonstrated its existence as monomer, trimer, or hexamer, with substrate-dependent equilibrium of homooligomer formation. In contrast, CES2 and CES3 exist as monomers. Both sequence aligments and secondary sequence predictions have suggested that these three CES are members of *α/β* hydrolase family[32–34]. Although the 3D structures of CES2 and CES3 have not been reported, the 3D structure modelling of both CES2 and CES3 can be downloaded from the SWISS-MODEL repository (a database of annotated 3D protein structure models generated by the SWISS-MODEL homology-modelling pipeline).

The molecular properties of CES1 and CES2 are listed in Table 1[6,9,19,25,27,29]. Similar to all reported serine hydrolases, the catalytic domain of human CEs contain a catalytic triad (such as Ser^{221}, Glu^{354}, and His^{468} in CES1) at the interface of the three domains, which is highly conserved among all mammalian carboxylesterases and is crucial for carboxylesterases-mediated catalysis (Fig. 1B)[9,27]. Mutation of any residue of the catalytic triad will lead to the loss of carboxylesterase activity[18]. Furthermore, the oxyanion hole formed by Gly^{142} and Gly^{143} in the HGGG motif is also highly conserved among all mammalian carboxylesterases and is essential for carboxylesterase activity. Notably, the active cavity of human CES1 is quite large (about 1,300 $Å^3$) and is lined mainly by hydrophobic amino acids, except the residues (such as Ser^{221}) of the catalytic triad. The residue Ser^{221} divides the whole ligand-binding pocket of CES1 into two pockets, one is a rigid pocket which makes CES1 selective for those substrates with small acyl group, and

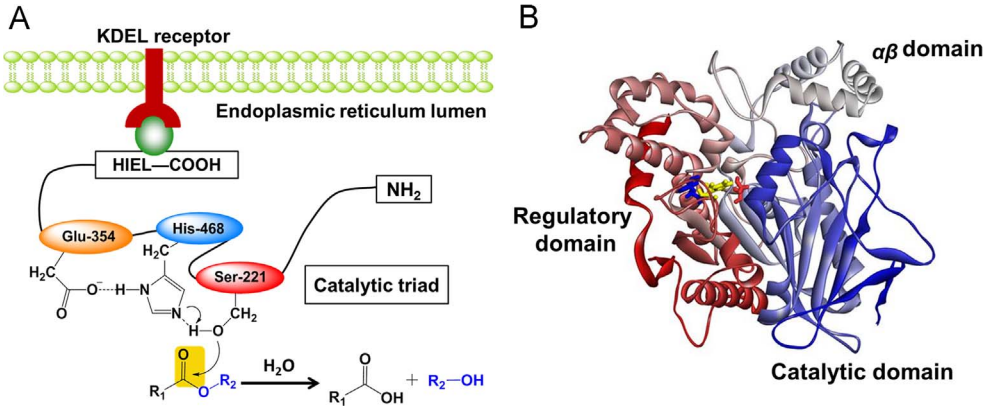

Figure 1 The structural features of CES1. (A) The scheme for catalyzing (hydrolysis) ester groups; (B) The 3D structure of CES1. The catalytic triad including Ser221, Glu354 and His468 are colored in red, yellow and blue, respectively.

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