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REVIEW ARTICLE

Structural diversity of carbohydrate esterases

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Abstract Carbohydrate esterases (CEs) catalyze the de-O or de-N-acylation by removing the ester decorations from carbohydrates. CEs are currently classified in 15 families in the Carbohydrate-Active Enzyme (CAZy) database, which classifies a large variety of enzymes that assemble, modify and breakdown carbohydrates and glycoconjugates. CEs have significant importance as biocatalysts in a variety of bioindustrial processes and applications. Thus, the understanding of molecular mechanisms involved in CE catalysis is essential. However, despite a rather large number of enzymes classified as CEs, just a few have been studied biochemically and only a handful has their three-dimensional structures determined and analyzed. Here, we present a brief overview of all currently classified CE families, mainly focusing on the structures and enzymatic activities of CEs.

Introduction

Hydrolytic enzymes that act on ester bonds, commonly termed esterases, are widely used as biocatalysts in industrial processes and biotechnology (Bornscheuer, 2002; Jaeger & Eggert, 2002; Jaeger & Reetz, 1998). The carbohydrate esterases (CEs) represent a class of esterases, which involves enzymes that catalyze the de-O or de-N-acylation to remove the ester decorations from carbohydrates (Cantarel et al., 2009). These enzymes are currently classified in 16 families in the Carbohydrate-Active Enzyme (CAZy) database, from CE1 to CE16. The CE family 10, however, has been nullified since most of the members of this family appeared to be esterases active against non-carbohydrate substrates, thus limiting the total number of CE families to 15.

The CAZy database (http://www.cazy.org/) is a curated database which systematically organize information about a large variety of enzymes that assemble, modify and breakdown carbohydrates and glycoconjugates, the CAZymes, classifying them according to their amino acid sequence similarities and common structural folds. This classification usually reflects enzymes mechanisms, protein fold and structural features better than specificity, grouping enzymes with different activities together in five large classes: Glycoside hydrolases (GHs), Glycosyltransferases (GTs), Polysaccharide lyases (PLs), Carbohydrate esterases (CEs), Auxiliary Activities (AAs). In addition, the Carbohydrate-binding modules (CBMs), which do not exhibit catalytic activity, are grouped together (Lombard, Ramulu, Drula, Coutinho, & Henrissat, 2014).

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The range of biological and biotechnological applications of CEs is diverse. For instance, the majority of families include members that catalyze the removal of ester-based modifications from mono-, oligo- and polysaccharides. Therefore, by removing the acylated moieties of polysaccharides, these carbohydrate esterases could accelerate the degradation of these polymers facilitating the access of glycosides hydrolases (GHs) (Christov & Prior, 1993) and assisting in biomass saccharification. This is relevant given the current scenario of energetic and environmental stress, leading to the implementation of renewable biofuels, sustainable materials and greed chemicals produced from biomass (Gupta & Verma, 2015). On the other hand, several CE families such as CE1, CE4, CE7, CE11 and CE14 contain enzyme targets for drug design and considerable potential in biomedical applications. These examples show the relevance of CEs in different branches of biotechnology and emphasize the importance of understanding of molecular mechanisms involved in CE catalysis. Here, we present a brief overview of all currently classified CE families, mainly focusing on their structures and enzymatic activities.

Carbohydrate esterase family 1

The CAZy Carbohydrate Esterase Family 1 (CE1) is one of the biggest and the most diversified CE family. The CE1 currently consists of 4746 proteins, mainly of bacterial origin (4593), including acetylxylan esterases (EC 3.1.1.72), feruloyl esterases (EC3.1.1.73), carboxylesterases (EC 3.1.1.1), S-formylglutathione hydrolases (EC3.1.2.12), diacylglycerol *O*-acyltransferases (EC2.3.1.20), and thehalose 6-*O*-mycolyltransferases (EC 2.3.1.122). There are 38 biochemically characterized CE1 enzymes and nine CE1 members with solved structures, seven bacterial proteins and two enzymes from eukaryotes. All CE1 solved structures adopt the α/β hydrolase fold, with topology characterized by a central β-sheet, with eight or nine β-strands, flanked on both sides by α-helices (Fig. 1A).

Among bacterial enzymes with known 3D structures, there are five mycolyltransferases, one from *Corynebacterium glutamicum*, the CgMytC (PDB id: 4H18; Huc et al., 2013) and four proteins of the *Mycobacterium tuberculosis* complex antigen 85 (ag85), ag85A (PDB id: 1SFR; Ronning, Vissa, Besra, Belisle, & Sacchettini, 2004), ag85B (PDB id: 1F0N; Anderson, Harth, Horwitz, & Eisenberg, 2001), ag85C (PDB id: 1DQZ; Ronning et al., 2000) and the non-catalytic protein MPT51 (PDB id: 1R88; Wilson, Maughan, Kremer, Besra, & Fütterer, 2004). Mycolyltransferase activity is essential for the biosynthesis of Gram-positive cell wall composed by mycolic acid, which involves transfer of the mycolyl group from α,α'-trehalose monomycolate (TMM) to a second TMM forming α,α'-trehalose dimycolate (TDM) (Belisle et al., 1997). It makes these enzymes a potential target for drugs and vaccines against tuberculosis (Horwitz, Lee, Dillon, & Harth, 1995; Prendergast et al., 2016).

Despite the presence of the carboxylesterase motif GXSXG (termed PS00120 in the PROSITE database) mycolyltransferases have transferase instead of hydrolytic activities. While hydrolytic mechanism of carboxylesterases utilizes a water molecule to hydrolyze the ester bond, the transferases use a hydroxyl group of an arabinose at the mycobacterial cell wall (Ronning et al., 2004). Structurally, these enzymes have an α/β fold, featuring a central β-sheet comprising between eight and nine β-strands, surrounded by five or six α-helices. All these enzymes utilize the Ser-His-Glu residues as a catalytic triad (Fig. 1A), instead of a most common Ser-His-Asp triad typical for carboxylic ester hydrolases. No additional domains have been observed for this group of enzymes.

The other three structures of CE1 family are classified as feruloyl esterases (EC 3.1.1.73), also known as cinnamoyl esterases or ferulic acid esterases (FAEs). Two enzymes are from *Clostridium thermocellum*, the FAE domain of the cellulosomal xylanase Z (FAE_XynZ, PDB id: 1JJF; Schubot et al., 2001), and the FAE of xylanase 10B (Xyn10B; PDB id: 1GKK; Prates et al., 2001). The third estarase is an eukaryotic FAE from the fungus *Anaeromyces mucronatus* (AmCE1/Fae1a, PDB id: 5CXU; Gruninger, Cote, McAllister, & Abbott, 2016). Xylan is a polymer that consists of $\beta(1 \rightarrow 4)$ xylosyl subunits and may be often decorated with arabinosyl residues, which could be decorated by the ferulic acids linked by an ester bond (Mueller-Harvey, Hartley, Harris, & Curzon, 1986). Ferulic acid, a hydroxycinnamic acid, crosslinks xylan, the

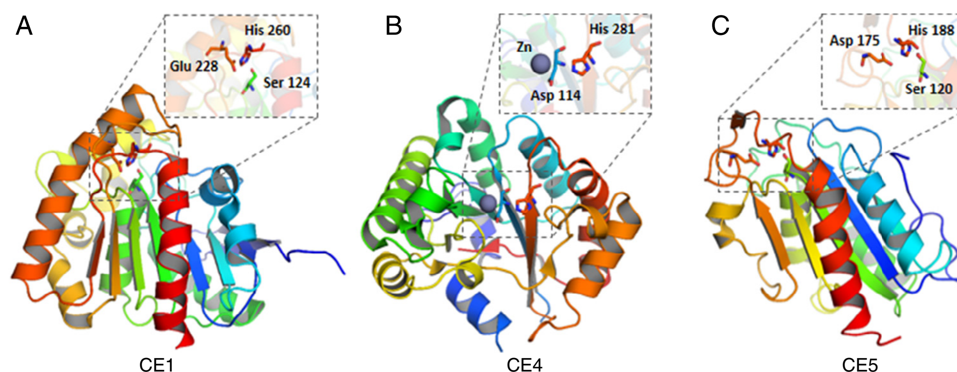

Figure 1 Representative 3D structures of the CE1, CE4 and CE5 members. Zooms into the active sites show catalytic residues displayed as sticks. (A) CE1 member, antigen 85C from *Mycobacterium tuberculosis* (PDB id: 1DQZ; Ronning et al., 2000). (B) PgdA, a peptidoglycan deacetylase from *Streptococcus mutans* from CE4 (PDB id: 2W3Z; Deng et al., 2009). (C) CE5 representative, a cutinase from *Fusarium solani* (PDB id: 1CUS; Martinez et al., 1992).

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