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The Magnificent World of Sulfatase and Sulfatase Maturating Enzymes

Prem Kumar Sinha*

Department of Biochemistry & Molecular Biology, The Pennsylvania State University, College of Medicine, Hershey, USA

The enzymes of sulfatase family (EC 3.1.6) are ubiquitously present across all domains of life and are involved in catalyzing hydrolysis of sulfate ester bonds for a vast array of substrates [1,2]. The substrates for these enzymes range from small cytosolic steriods, like estrogen sulfate, to complex cell surface carbohydrates, such as the glycosaminoglycans. 17 sulfatases have been identified in humans, with 14 of them known to be associated with specific catabolic activities [1,2]. Sulfatases have been linked with various pathophysiological conditions including, lysosomal storage disorders, developmental abnormalities, and bacterial pathogenesis [1,2]. Biological importance of sulfatases is further manifested by several inherited metabolic diseases in humans, including metachromatic leukodystrophy, mucopolysaccaridosis VI, ichthyosis, which are all known to occur due to deficiency of specific single sulfatases [3]. Moreover, the activities of all sulfatases are severely reduced in a rare inherited disorder named multiple sulfatase deficiency (MSD) [3]. Sulfatases from different enterobacteria such as, *Klebsiella*, *Salmonella, Enterobacter, Proteus, Serratia* and various pseudomonads like, *Pseudomonas, Comamonas,* and *Mycobacteria* have been subjects of wide studies [1, 2]. Inhibition of sulfatase activity has been shown to result in inability of the prominent human gut symbiont in colonizing the mucosal layer of host's gut [4]. Distinctive sulfatase fingerprints form the basis for judging the species and lineage in mycobacterial strains [5]. Recently, Beatty et al. [5] developed a sulfatase-activated probe for rapid detection of sulfatases in mycobacterial lysates based on the detection of enzymatic activity in native protein gels.

Though sulfatases have been classified into three different classes, type I family members are most common and the only class existent in eukaryotes. X-ray crystal structures of known group I sulfatses [human arylsulfatase A (ASA), arylsulfatase B, arylsulfatase C and bacterial arylsulfatase from *Pseudomonas aeruginosa* (PAS)], all show striking similarity, with superimposable catalytic polar domain, nearly spherical globular monomeric structure and mixed α/β topology [6]. Based on high sequence similarity and structural likeness, type I sulfatases are considered to have emerged from one common ancestral gene [1,2,7]. A highly conserved N-terminal region encompassing consensus sulfatase motifs and a unique posttranslational modification are essential features of the members of sulfatase enzyme family. The critical posttranslational modification, which is absolutely essential for the catalytic activity of sulfatases, involves conversion of a cysteine or a serine residue to 2-amino-3-oxopropanoic acid [Cα-formylglycine (FGly)], in a conserved active site-localized sequence motif (C/SxPxRxxxLTGR) [8]. This aldehyde-functionalized FGly residue is directly involved in the catalytic mechanism for sulfate ester hydrolysis.

Sulfatase genes are principally clustered with the sulfatase modifying factors (SUMF), which are distinct among different domains of life [7]: (i) Formylglycine-generating enzymes (FGEs) found in eukaryotes and certain prokaryotes, are cofactor-independent aerobic enzymes [9,10]; (ii) Anaerobic sulfatase maturating enzymes (anSME) found exclusively in prokaryotes, are iron-sulfur containing radical *S*-adenosylmethionine (SAM) enzymes that modify both serine-type and cysteine-type sulfatases [11-13]. FGEs are broadly classified as cofactor-less cysteine-dependent oxidase/oxygenase. The crystal structure of human FGE showed novel-fold, the so called "FGE-fold', demarcated by one domain of low secondary structure content [9]. The structure of the *Mycobacterium tuberculosis* FGE ortholog from *Streptomyces coelicolor* showed remarkable structural similarity to human FGE, including the position of catalytic cysteine residue and FGE-fold, which was later classified as a subtype of the C-type lectin fold [10]. Regulation of mammalian FGE activity is mediated through several protein-protein interactions (known protein partners include PDI, ERGIC-53, ERp44) in the ER and Golgi [14]. In the prokaryotic world, the sulfatase modifying machineries were principally categorized as cysteine or serine-type based on the target residue in sulfatase that gets modified to FGly. The cysteine-type anSME from *Clostridium perfringens* and serine-type anSME from *Klebsiella pneumonia* have been the subjects of broad studies, with the two enzymes sharing about 48% sequence similarity [11-13]. In a pioneering work, Benjdia et al. [11] showed the evidence that anSME belongs to radical AdoMet enzyme family that uses a 5'-deoxyadenosyl radical to directly catalyze H-atom abstraction from an active site cysteinyl or seryl residue. Another compelling study recently reported that anSME could convert cysteine, serine, and selenocysteine residues to FGly, as well as threonyl residues to the corresponding keto product, suggestive of commonality in the catalytic mechanism [13].

The observation that human FGE recognizes its substrates based solely on primary sequence i.e. (C/S)xPxR motif, laid the groundwork for the development of a small peptide tag based on the sulfatase motif (termed the aldehyde tag) offering precise chemical control, thus directing FGly formation independent of its context [15]. Consequently, this field is witnessing huge biotechnological surge empowering the development of new protein products for research and therapeutic purposes based on the genetically encoded chemical tag [16]. Further progress in this field would certainly shed more light towards understanding and appreciating sulfatase and sulfatase maturating enzymes, the two magnificent enzymes in the majestic world of nature's enzyme evolution and catalytic strategy.

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***Corresponding author:** Prem Kumar Sinha, Department of Biochemistry & Molecular Biology, The Pennsylvania State University, College of Medicine, Hershey, USA, E-mail: pks14@psu.edu

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