Molecular Basis for MSD and Catalytic Mechanism of the Human Formylglycine Generating Enzyme

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Sulfatases are enzymes essential for degradation and remodeling of sulfate esters. Formylglycine (FGly), the key catalytic residue in the active site, is unique to sulfatases. In higher eukaryotes, FGly is generated from a cysteine precursor by the FGly generating enzyme (FGE). Inactivity of FGE results in multiple sulfatase deficiency (MSD), a fatal autosomal recessive syndrome. We determined the FGE crystal structure by Ca^{2+}/Sulphur SAD phasing using in-house data collected at a wavelength of 1.54Å. Based on this structure, we report that FGE is a single-domain monomer with a surprising paucity of secondary structure and adopts a unique fold. The effect of all eighteen missense mutations found in MSD patients is explained by the FGE structure, providing a molecular basis of MSD. The catalytic mechanism of FGly generation was elucidated by six high-resolution structures of FGE in different redox environments. The structures allow formulation of a novel oxygenase mechanism whereby FGE utilizes molecular oxygen to generate FGly *via* a cysteine sulfenic acid intermediate [1].

[1] Dierks T., Dickmanns A., Preusser-Kunze A. Schmidt B., Mariappan M., von Figura K., Ficner R., Rudolph M.G., *Cell*, 2005, **121**, *in press.*

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