A versatile oxygenase family

Enzymes catalyze important biological processes throughout all kingdoms of life. One large and highly versatile enzyme family possesses a three-dimensional structure containing a double-stranded beta-helix (or jellyroll) protein fold that typically has a 2-histidine-1-carboxylate amino acid motif for binding ferrous ion (Fig. 1). This metal center interacts with 2-oxoglutarate and oxygen, resulting in the formation of succinate, carbon dioxide, and a highly reactive Fe(IV)-oxo (or ferryl) intermediate. Members of this oxygenase family use the ferryl intermediate to oxidize their primary substrate to achieve a remarkable range of catalytic reactions (Fig. 2).

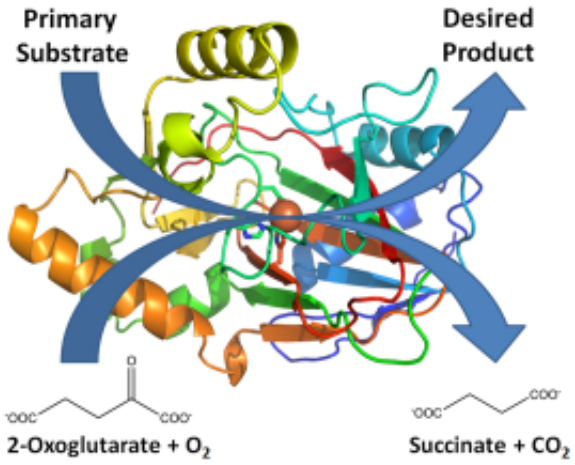

Fig. 1. Representative structure, active site, and general reaction of a 2-oxoglutarate dependent oxygenase.

Many 2-oxoglutarate dependent oxygenases use the ferryl intermediate to insert an oxygen atom into a C-H bond, a hydroxylase reaction, as extensively studied using TauD—an enzyme that decomposes taurine, a biological sulfonate. Analogous chemical steps are responsible for the modification of prolyl residues in the structural protein collagen, oxygen sensing by other prolyl hydroxylases, repair of alkylation damage in DNA and RNA, histone demethylations related to epigenetic regulation, and many other transformations.

A closely related series of reactions is carried out by halogenases that install a halogen atom (e.g., chlorine or bromine) to replace a hydrogen atom in a C-H bond. For example, SyrB2 decomposes 2-oxoglutarate and consumes oxygen while adding a chlorine atom to L-threonine to make 4-Cl-L-threonine (when connected to a carrier protein called SyrB1) in syringomycin E synthesis. The iron atom in these enzymes is bound to a 2-histidine motif, with the carboxylate found in other family members replaced by an alanine residue.

Fig. 2. Types of transformations catalyzed by the 2-oxoglutarate dependent oxygenases.

Several types of oxygenase reactions are utilized for synthesis of antibiotics. For example, clavaminate synthase (CAS) catalyzes hydroxylation, ring formation, and double bond formation (desaturation) during ?-lactam biosynthesis. In addition, carbapenam synthase (CarC) catalyzes desaturation and epimerization (inversion of a stereocenter) while deacetoxycephalosporin C synthase (DAOCS) catalyzes ring expansion of related compounds. Each of these reactions is critical for making the target group of antibiotics.

Other members of this enzyme family use related chemistries to generate a wide array of additional metabolites with diverse functions in plants, fungi, and bacteria. As just two examples, hyoscyamine 6?-hydroxylase (H6H) from henbane creates a three-membered epoxide ring in a hallucinogenic tropane alkaloid and FtmOx1 from a fungus joins two alkyl groups via endoperoxidation (forming an R-O-O-R linkage) in a mycotoxin.

Clearly, oxygenases using ferrous ion and 2-oxoglutarate are capable of catalyzing a wide range of chemical reactions that transform their target substrates into a diverse set of biologically important compounds.

Publication

Catalytic Mechanisms of Fe(II)- and 2-Oxoglutarate-dependent Oxygenases.
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