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Review article

Structural studies on 2-oxoglutarate oxygenases and related double-stranded β-helix fold proteins

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Abstract

Mononuclear non-heme ferrous iron dependent oxygenases and oxidases constitute an extended enzyme family that catalyze a wide range of oxidation reactions. The largest known sub-group employs 2-oxoglutarate as a cosubstrate and catalysis by these and closely related enzymes is proposed to proceed via a ferryl intermediate coordinated to the active site via a conserved HXD/E...H motif. Crystallographic studies on the 2-oxoglutarate oxygenases and related enzymes have revealed a common double-stranded β-helix core fold that supports the residues coordinating the iron. This fold is common to proteins of the cupin and the JmjC transcription factor families. The crystallographic studies on 2-oxoglutarate oxygenases and closely related enzymes are reviewed and compared with other metallo-enzymes/related proteins containing a double-stranded β-helix fold. Proposals regarding the suitability of the active sites and folds of the 2-oxoglutarate oxygenases to catalyze reactions involving reactive oxidizing species are described.

Keywords: Cupin; Double stranded β-helix; DSBH; Iron coordination; JmjC; Metallo-enzyme; Non-heme iron; 2-Oxoglutarate; Oxygenase; Protein structure

1. Introduction

The non-heme and Fe^{II} dependent oxygenases and oxidases are an extended superfamily of enzymes that catalyze a diverse range of oxidation reactions. Members of the largest known sub-group of these enzymes utilize 2-oxoglutarate (2OG) as a cosubstrate and share a conserved fold and Fe^{II} binding motif (for reviews see [1–9]). The mechanisms of all the 2OG oxygenases and related oxidizing enzymes are also all proposed to employ a high valent iron-oxo (ferryl) species that effects oxidation of the substrate [10].

The chemically interesting oxidation reactions catalyzed by Fe^{II} and 2OG dependent oxygenases and the importance of certain family members in medicinally relevant processes has motivated studies on their diverse mechanisms and structures (Fig. 1). Following from crystal structures of the members of the family involved in β-lactam antibiotic biosynthesis [11,12] many more crystal structures have been reported (Table 1). This review initially summarizes the range of reactions and medicinal relevance of the 2OG oxygenases then focuses on structural studies of the family. The mechanistic and functional insights that the structural work has provided are discussed including a description of the environment in which the ferryl and other proposed reactive oxidizing intermediates are generated and react. The review updates previous reports on structural aspects of 2OG oxygenases [3,13] and aims to complement other reviews that center on non-structural aspects of mechanistic studies on 2OG oxygenases, on di-iron dependent oxygenases, and on other families of

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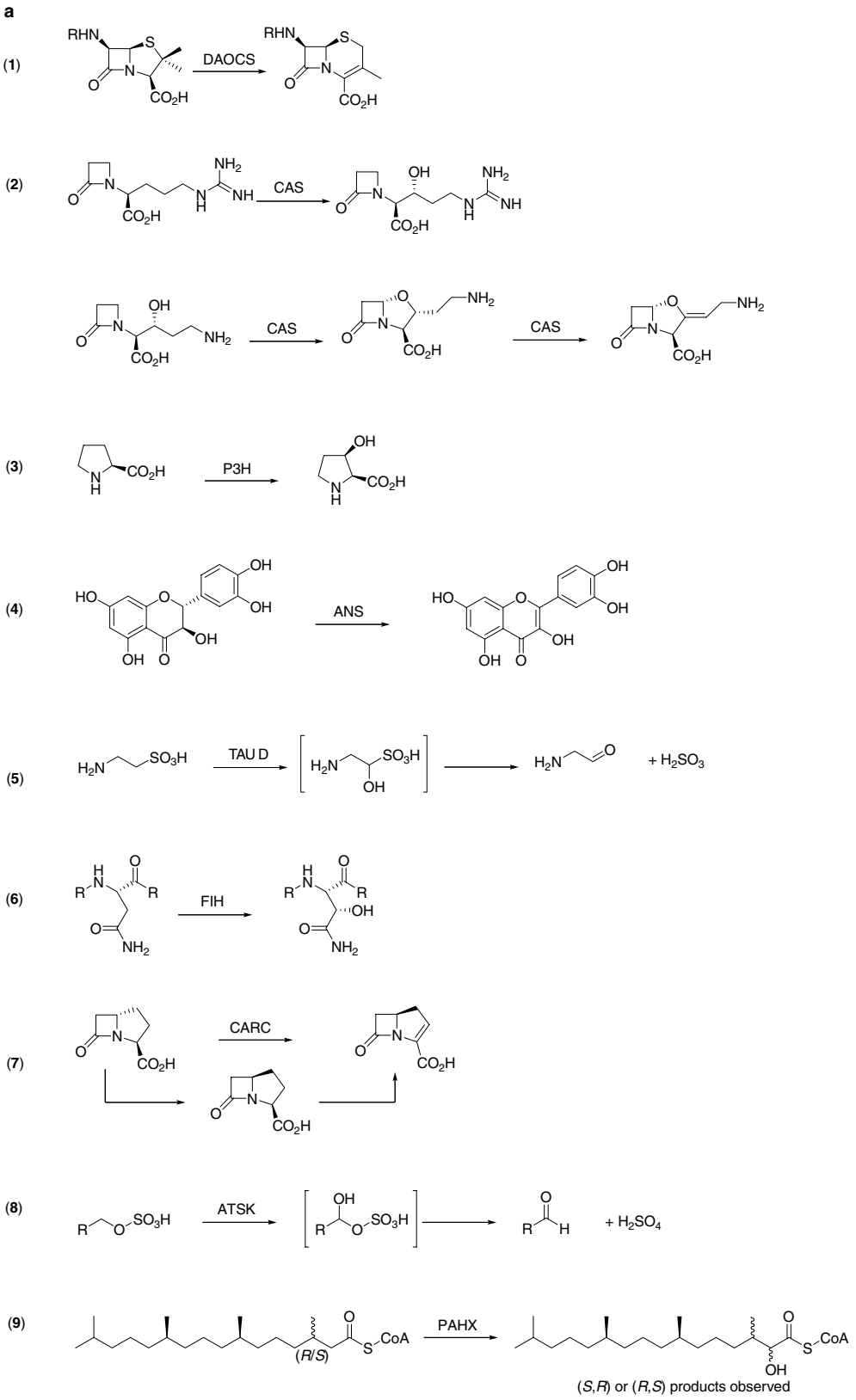

Fig. 1. Reactions catalyzed by 2OG oxygenases and several related DSBH enzymes for which crystallographic structures are available. The numbers to the left of each scheme, and abbreviations for enzymes correspond to those in Table 1. (a) Reactions catalyzed by 2OG dependent oxygenases. Each reaction is coupled to the conversion of O_2 and 2OG to succinate and CO_2. Additional products are not shown for clarity. (b) Reactions catalyzed by DSBH oxidizing enzymes closely related to the 2OG oxygenases. (c) Reactions catalyzed by DSBH containing redox enzymes not closely related to the 2OG oxygenases. Each enzymes uses O_2 as a co-substrate. (d) Reactions catalyzed by DSBH containing and metal binding non-redox enzyme.