

Preface

In the 1960s scientists discovered three examples of 2-oxoglutarate (2OG)-dependent oxygenases catalysing the hydroxylation of (i) prolyl residues in collagen precursors, (ii) the free base thymine and (iii) γ -butyrobetaine. During the intervening 50 years or so, a remarkably broad diversity of alternate reactions and substrates has been revealed for the 2OG-dependent oxygenases and extensive advances have been achieved in our understanding of their structures and catalytic mechanisms. These mononuclear Fe(II) enzymes most often catalyse hydroxylation reactions, but other types of chemistries are known including dealkylation, desaturation, cyclization and halogenation reactions. These reactions are employed in a variety of biological roles including the biosynthesis of cellular components, the generation of important small molecules including widely used antibiotics, the disposal of undesired molecules, and in regulatory processes such as hypoxic signaling. 2OG-dependent oxygenases are also important agrochemical targets and are being pursued as therapeutic targets for a wide range of diseases including cancer and anaemia. Given the numerous recent advances and biomedical interest in this field, we recognized the utility of compiling a series of in-depth reviews of these enzymes in a single text. Our hope is that such a timely compendium will be a valuable resource and serve to unite and stimulate the field.

This book offers an overview of the rapidly evolving field of research involving 2OG-dependent oxygenases. We begin with four broad summary chapters that highlight critical aspects of this field. Chapter 1 (Hausinger) explores the vast enzymatic landscape associated with the amazingly diverse set of reactions catalysed by 2OG-dependent oxygenases. An overview of the conserved structural platform and metallocentres employed by 2OG-dependent oxygenases is presented in Chapter 2 (Schofield and colleagues). Advances

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in our mechanistic understanding of these enzymes, including information on the key intermediates, are highlighted in Chapter 3 (Bollinger, Krebs and coworkers). Biomimetic analogues that have been helpful in dissecting the mechanism and metallocentre properties, and which may ultimately enable the discovery of novel catalysts, are described in Chapter 4 (Que and colleagues). These overview discussions set the stage for an additional 17 chapters focused on carefully targeted topics.

The substrates for many 2OG-dependent oxygenases are macromolecules, including proteins, lipids and oligonucleotides. Hydroxylases acting on prolyl and lysyl residues in pro-collagen are presented in Chapter 5 (Mylyharju). Chapter 6 (Schofield and coworkers) describes work on other protein hydroxylases that play a central role in hypoxic signalling in animals. The very rapidly developing field, from both biochemical and physiological perspectives, of 2OG-dependent oxygenases (the JmjC enzymes) that remove methyl groups from lysyl-derived side chains *via* oxidative dealkylations is described in Chapter 7 (Cheng and Trievel). Chapter 8 (Müller and Hausinger) summarizes knowledge of the DNA/RNA repair enzyme AlkB that catalyses the dealkylation of modified bases and its ALKBH mammalian homologues. Related oxygenases acting on nucleic acids are then described, *i.e.* two RNA-specific demethylases, FTO and ALKBH5, in Chapter 9 (Zheng and He) and ALKBH8 and its role in synthesis of a modified tRNA in Chapter 10 (Falnes and Ho). The series of ten-eleven translocase (TET) oxygenases that oxidize 5-methylcytosine in DNA, and which have been attracting substantial biomedical interest, is described in Chapter 11 (Aravind and associates). Finally, the conversion of the thymine base within DNA into the novel base J (β -D-glucopyranosyloxymethyluracil) by one of these enzymes in selected protozoa is detailed in Chapter 12 (Sabatini and colleagues).

A multitude of other 2OG-dependent enzymes utilize small molecule substrates and function in diverse roles that include lipid metabolism or synthesis of plant signalling molecules and antibiotics. Chapter 13 (Vaz and van Vlies) details two enzymes involved in the biosynthesis of carnitine, which plays a central role in fatty acid metabolism in animals. The metabolism of the chlorophyll metabolite phytanic acid by a 2OG-dependent hydroxylase is described in Chapter 14 (Wanders and colleagues). The roles of selected enzymes during the biosynthesis of flavonoids and gibberellins are summarized in Chapter 15 (Martens and Matern) and Chapter 16 (Hedden and Phillips), respectively. Chapter 17 (Andersson and Valegård) and Chapter 18 (Smith and Khare) cover roles of 2OG-dependent oxygenases in the biosynthesis of the medicinally important cephalosporin antibiotics and various halogenated molecules, respectively.

Several enzymes are structurally and mechanistically related to the 2OG-dependent oxygenases, but do not utilize 2OG as a cosubstrate. Chapter 19 (Rutledge) summarizes the amazing chemistry of isopenicillin *N* synthase, which catalyses a unique bicyclization reaction. Formation of the agriculturally important plant signalling molecule ethylene is catalysed by 1-aminocyclopropane-1-carboxylate oxidase as described in Chapter 20 (Simaan and

Réglier). Finally, two enzymes that produce distinct products from an alternative 2-oxo acid, 4-hydroxyphenylpyruvate, and their commercial importance, are detailed in Chapter 21 (Shah and Moran).

We sincerely thank all of the authors for their outstanding contributions, which reveal the current states of understanding in this ever-expanding field of research. We apologize for the incomplete coverage due to space constraints. We hope the book will stimulate further research on the functions of 2OG-dependent oxygenases at levels ranging from the biochemical to the physiological and hope it may in a small way help to enable translation of the basic science into medicinal and agricultural benefits. Finally, we feel that there surely must be more roles and amazing reactions catalysed by 2OG-dependent oxygenases waiting to be discovered.

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