A short history of heme dioxygenases: rise, fall and rise again

Emma L. Raven

In the beginning there were two

As often happens, two people drew more or less the same conclusions at more or less the same time. In 1955, Mason [1] and Hayaishi [2, 3] independently proposed that enzymatic incorporation of molecular oxygen into a substrate was possible. At the time, this was an almost unthinkable idea—probably because the prominent German chemist and Nobel Prize winner Heinrich Wieland (and naturally, therefore, almost everybody else) had ruled the possibility out—but this did not stop Mason and Hayaishi thinking about it quite a lot.

Mason’s experiment was published in 1955 [4] and led to his now famous classification of enzymatic oxygen metabolism [5]. Mason proposed that two atoms of molecular oxygen can be incorporated into the substrate and he termed this type of activity an “oxygen transferase”. Hayaishi, using mass spectrometry, demonstrated quantitative incorporation of $^{18}$O$_2$ (and, importantly, not H$_2^{18}$O) into the substrate in the pyrocatechase reaction [6]. He too referred to the activity as “oxygen transferase”. Hayaishi, Fig. 1, later introduced the term “oxygenase” to the literature [7], a proposal that had first been mooted at an ACS meeting in 1956 [8] and which has stuck in the heme literature ever since.

In the beginning there were two

Power to the people

There are fashions in science, just as there are in styles of trousers. Fashions in science are influenced by variables large and small: governments that can control the political climate; policy and funding streams; universities and other institutions that control scientific appointments; geography that can enhance or restrict access to ideas or technology; and the rate of development of technology itself which can either slow down or suddenly speed up scientific progress. But more often than not, fashions in science are also influenced to a greater or lesser extent by people, for it is the people who create the focus, the scientific stimulus, and the new ideas upon which future progress must be based.

In the case of the heme dioxygenase enzymes, a handful of people were highly influential and they laid the foundations for the development of the area over the next 60 years. This short perspective summarises these and other early contributions to the heme dioxygenase field.

Where there’s muck there’s brass

Hayaishi’s introduction to tryptophan metabolism had occurred from a chance encounter at Osaka University with Kotake. Kotake had devoted much of his life’s work to the biochemistry of that particular amino acid in animals and had published some of the earliest seminal studies in the 1930s [9, 10], Fig. 2. Japan at that time was in the
aftermath of the war, and Osaka had been totally demolished. Kotake, perhaps wishing to see the tradition of a Japanese effort in the tryptophan area continued into the future, donated several grams of the precious compound to Hayaishi. With no chemicals, no equipment to speak of, a non-existent consumables budget, no animals and probably no students either, Hayaishi has pointed out [2] that his options were somewhat limited. By necessity, he went outside and, literally, dug up some muck and mixed it with his compound. From there he was able to demonstrate that certain microorganisms in soil can grow using tryptophan, and what followed was a series of four consecutive papers all looking at enzymatic incorporation of O₂ into a substrate [7, 11–13]. One of these, Fig. 3 [11], concerned itself with the oxidation of tryptophan and examined the conversion of tryptophan to \( \text{N-formylkynurenine (NFK)} \) in \textit{Pseudomonas} extracts using mass spectrometry, Scheme 1. It was the first demonstration that “…both atoms of oxygen incorporated in the oxidative step are derived from oxygen gas but not from water” [11].

At that time, the metabolism of tryptophan was just beginning to be clarified, and several people—including the distinguished A. Neuberger from Mill Hill in London—[14, 15]—had come to the conclusion that NFK was part of the process. But the enzyme responsible for the activity had not been fully established, and it had been temporarily denominated as a “tryptophan peroxidase”. The early nomenclature, to put it mildly, would send shivers down the spine of an IUPAC committee. A list of terms as long as the Royal Mile appeared in print: tryptophan pyrrolase (which still pervades in the literature), tryptophan peroxidase, tryptophan oxidase, tryptophan peroxidase-oxidase, and tryptophan oxygenase were all used (see for example [14, 16–22]). Most authors evidently found the process of deciding between these terms to be an impossible task and so used them all at the same time. It was Hayaishi himself who brought some order to the confusion, by suggesting in 1970 [23] that the enzyme would most sensibly be named tryptophan 2,3-dioxygenase (TDO), to distinguish its reactivity from any other enzymatic tryptophan activity (e.g. in the formation of tryptophan 5-monooxygenase). Even so, it took some years before the literature adjusted to this brave new world in which one enzyme had only one name.

It had been known at this time that there were other enzymes from different sources capable of catalysing the oxidation of tryptophan to NFK, as catalysed by IDO and TDO.

Fig. 1 Professor Hayaishi pictured holding a model of the fictional hero Don Quixote, of whom he was a long-standing admirer (see [113]). The photograph was provided by Hayaishi’s daughter, via his former secretary, to Prof. Masao Ikeda Saito

Fig. 2 One of the seminal (but for some readers somewhat impenetrable) papers from Kotake [10]

Fig. 3 Hayaishi’s seminal paper [11] reporting that both atoms of oxygen incorporated into the product during tryptophan oxidation are derived from \( ^{18}\text{O}_2 \). Reproduced with permission from The American Society for Biochemistry and Molecular Biology

Scheme 1 The oxidation of tryptophan to NFK, as catalysed by IDO and TDO

1 Fred Sanger was Neuberger’s first Ph.D. student.
same reaction as TDO, but with much less substrate specificity than TDO. As far back as 1967, Hayaishi had identified one such enzyme from rabbit intestine [17] and it was initially identified as “tryptophan pyrrolase (tryptophan 2,3-dioxygenase)”. In view of the broad substrate specificity of these other enzymes, it was suggested [24], again by Hayaishi, that they be designated as indoleamine 2,3-dioxygenases (IDO), to differentiate them from the TDOs (which are specific for tryptophan) and to convey the message that other substituted indoles were also accessible by these enzymes. Although even as late as 1974 the community was still afflicted by chronic indecision on the names for their pet enzymes, as the early proposal [24] also suggested the very awkward and certainly confusing “indoleamine 2,3-dioxygenase (pyrrolase)” nomenclature. But by the end of the 1970s the literature was more consistent, with regular papers describing the properties of the now easily recognisable indoleamine 2,3-dioxygenase enzyme (see for example [25–34]).

In the intervening years, a much clearer picture has emerged. It is now well known that the IDOs and the TDOs, whilst catalysing the same reaction, have slightly different properties. IDOs are monomeric, while the TDOs are tetrameric. IDOs have wide substrate specificity and will oxidise a range of indoleamine derivatives, while the TDOs are much more discriminating and typically oxidise only L-Trp at any respectable catalytic rate. Also, while IDO is widely distributed in all tissues but not the liver, TDO has most often been cited as being found only in the liver (although there is emerging evidence that it is also located in some cancer cells [35]).

The 1970s: the emergence of heavy metal

The idea that there could be a role for a metal in tryptophan oxidation took a while to sink in. The earliest mention of a heme dependency that this author was able to identify came in 1959 (and there were indications even earlier than that [36]). Tanaka and Knox [16] presented UV–visible spectra for the TDO from rabbit liver, Fig. 4, with Soret bands that are surprisingly close to those found for recombinant mammalian TDOs and bacterial TDOs isolated many decades later [37–43], and they suggested a similarity with the by then well-known ferrous oxy hemoglobin system. A series of papers from Feigelson going back as far as 1961 also demonstrated very fluently that the activity of TDO was dependent on heme (see for example [20, 21, 44–47]). By the late 1970s, the role of heme had finally become “mainstream” in the IDO literature as well [29–34].

The suggestion [22, 48] that copper was involved in TDO catalysis turned out not to be correct [49, 50], but nonetheless generated heated debate.

The 1980s onwards

In the 10 years or from 1980, after the extensive work that had been done previously (as summarised above), a large volume of spectroscopy and kinetic work appeared on both IDO and TDO. This has been comprehensively summarised in an outstanding review by Sono and Dawson in 1996 [18] and will not be rehearsed here again. But an analysis of the literature, Fig. 5, shows that there was a lull in publication activity around the late 1980s and early 1990s. The field stalled to some extent, waiting for the development of suitable systems for expression of IDO and TDO in E. coli. An early report [37] of expression of rat TDO in E. coli stood out and led the way as it preceded, by some margin, the publication of numerous other expression systems for TDO/IDO in mammalian [38–40, 51–60], bacterial [61–63], insect [64–66], fungal [67, 68], yeast [67] and other [69] systems.

A new dawn from 2000: arise again

The Dawson review was very timely, because it included a focused but detailed summary of all of the previous IDO and TDO work. With expression systems emerging soon afterwards (see above), the review set the scene for a resurgence in interest in these enzymes over the next two decades, Fig. 5. Mauk has referred to this as a “renaissance” [70]. Much of the new work in the last few years has been motivated by the search for IDO inhibitors relevant to therapeutic application in cancer [71–73].
Mechanism

Techniques other than crystallography have been needed to make progress on mechanism, and there is much work to do yet before the mechanism is fully clarified. Early proposals for the mechanism of NFK formation [87] have been substantially revised in recent years. The generational echoes have resonated loudly, as some of the newer ideas on mechanism [88] were derived from mass spectrometry experiments (as in the early days [6]).

Spectroscopy and kinetics, at one time the poor relations compared to the mighty crystallography, are now playing a leading role again just as they did in the 1980s (including recently on indoleamine 2,3-dioxygenase 2 (IDO-2) [89]). In terms of mechanism, there seems to be a consensus emerging that the mechanism outlined in Fig. 6 is reasonable, but things are far from being conclusively established and, bearing in mind the early mechanistic red herrings in this area [87], caution is still needed. Computational approaches have proved very useful in elucidating the mechanism [90–93].

Early proposals [87] for tryptophan oxidation suggested a base-catalysed abstraction mechanism and no change in oxidation state of the metal, but several groups had independently reported [42, 88, 94] that the 1-Me-\textsuperscript{t}-Trp analogue was also reactive, and it was noted [95] that this is not consistent with a base-catalysed abstraction mechanism. Mutational data where the presumed active site base (histidine) had been removed were also not consistent with base-catalysed abstraction [96]. Two other mechanisms, Fig. 6, have been put forward [88, 90, 91, 97], but there is little in the way of firm evidence for either. Electrophilic addition from the ferrous oxo species, Fig. 6, is one possibility: recent evidence in TDO [98] (using modified hemes that were first used more than 30 years ago [99]) supports this. We have noted [74, 75] that oxygen may not be an especially good electrophile if it is bound to the heme as a ferric superoxide species, and there is spectroscopic evidence for a ferric superoxide species [97] from Raman’s work. An alternative suggestion [97] is radical addition from the ferric superoxide, Fig. 6 (bottom). Both pathways lead to formation of a ferryl (Fe\textsuperscript{IV}) species. There is mass spectrometry evidence for epoxide formation [100], but later intermediates in the mechanism are not clarified. Addition of oxygen across either the C\textsuperscript{2} or the C\textsuperscript{3} position of the substrate is possible for both the radical and electrophilic mechanisms, and at present this is a moot point. Both possibilities have been suggested [82, 88, 90, 91, 93, 97].

A real step forward was made using resonance Raman [97, 101] to identify a ferryl (Compound II) intermediate in the IDO mechanism. The same Compound II species has recently been identified kinetically and is also observed during oxidation of 1-methyl-\textsuperscript{t}-Trp and a number of other substrate analogues [102], providing strong evidence that IDO uses the same mechanism for oxidation of tryptophan as it does for oxidation of other substrate...
analogue. We have argued [74, 75, 103] that since the process of oxygen activation in most heme enzymes (e.g. P450s, peroxidases, etc.) is also achieved through formation of highly oxidised iron intermediates, this brings the dioxygenases into line with the oxidative mechanisms used in other heme enzymes, as illustrated schematically in Fig. 7. One difference in the dioxygenases is that continuous re-reduction of an oxidised ferryl heme (through an associated reductase) is not required, because all of the available evidence indicates that the dioxygenases only require a single, initiating reduction of ferric heme. The reader is referred to previous reviews [74, 75, 103] for a fuller discussion.

Substrate binding and catalysis

It had been noted from very early on [17, 104] that the rate of tryptophan turnover in IDO decreases at high concentrations of substrate. This was originally proposed [104] to be a consequence of substrate binding to the ferric form of the enzyme, but this is not consistent with the known [51, 105] increase in reduction potential on substrate binding and has therefore been questioned [106]. Some evidence suggests that the sequence of binding of O₂ and the substrate at high and low substrate concentrations is important [106–108], possibly linked to changes in the reduction potential on substrate binding [106]. Others have suggested [94] that there is a second (inhibitory) binding site in IDO and that this is the origin of the inhibition—this is also plausible and there is evidence for more than one binding site (or at least multiple binding conformations) [61, 109–112], including in a recent structure for human TDO where a second l-Trp binding site (referred to as an exo site) has been clearly observed at >40 Å from the active site [82].

What goes around comes around: the lasting contribution of Osamu Hayaishi

Heme dioxygenases have floated into fashion, out of it, and back in again. The early contributions that Hayaishi made to the dioxygenase field are a lasting legacy that form a framework of reference to this day and will serve us all well as the field moves to the future.

Fig. 6 A mechanism for tryptophan oxidation, consistent with all of the recent observations. Electrophilic addition (top) and radical addition (bottom) are possible. See text for details. Recent structural information [82] indicates that NFK is bound to the iron in the enzyme–product complex.
A comparison of mechanisms of oxygen activation in different heme enzymes. The well-known peroxidase mechanism (blue arrows) goes via ferric heme directly to Compound I and then to Compound II by one electron oxidation of substrate [114]. The P450s (purple arrows) use the same Compound I species but they access it through the ferrous oxy species by one electron reduction, and by rebound mechanisms access the same Compound II species [115, 116]. The identification [97, 101, 102] of a Compound II species in IDO (which accumulates in the steady state) aligns the dioxygenase mechanism (orange arrows) with these established patterns of reactivity in other heme systems. It has been assumed that IDO and TDO react by the same mechanism, but Compound II in TDO has never been detected in the steady state. There is evidence that the absence of Compound II in the steady state in TDO might be due to a change in the rate-limiting step in TDO compared to IDO, such that Compound II does not accumulate [117]. Note that there is also evidence [118] that IDO can exhibit indole peroxidase activity (i.e. a peroxide-dependent insertion of oxygen into indole), similar to the well-known peroxide shunt of the P450s.

Acknowledgements ER acknowledges Dr. J. Basran (University of Leicester), Dr. I. Rowlands (University of Leicester Library), and Prof. Almira Correia for helpful discussions.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. (2016) Revealing the impact of oxygen on molecular biology: the work of Howard Mason. J Biol Chem 291(18):9851–9852. doi:10.1074/jbc.O116.000002

2. Hayaishi O (2008) From oxygenase to sleep. J Biol Chem 283:19165–19175

3. Kresge N, Simoni RD, Hill RL (2005) Pioneering the field of oxygenases through the study of tryptophan metabolism: the work of Osamu Hayaishi (Reprinted). J Biol Chem 280

4. Mason HS, Fowlks WL, Peterson E (1955) Oxygen transfer and electron transport by the phenolase complex. J Am Chem Soc 77:2914–2915

5. Mason HS (1957) Mechanisms of oxygen metabolism. Science 125:1185–1188

6. Hayaishi O, Katagiri M, Rothberg S (1955) Mechanism of the pyrocatechase reaction. J Am Chem Soc 77:5450–5451

7. Hayaishi O, Katagiri M, Rothberg S (1957) Studies on oxygenases; pyrocatechase. J Biol Chem 229:905–920

8. Hayaishi O, Rothberg S, Mehler AH (1956) Abstracts, 130th ACS meeting, Atlantic City. 53C

9. Kotake Y, Iwao J, Kujokawa M, Ichihara K, Otani S, Tsujimoto J, Sakata H (1931) Z Physiol Chem 195:139–192

10. Kotake Y, Masayama I (1936) The Intermediary metabolism of tryptophan. XVIII. The mechanism of formation of kynurenine from tryptophan. Z Z Physiol Chem 243:237–244

11. Hayaishi O, Rothberg S, Mehler AH, Saito Y (1957) Studies on oxygenases; enzymatic formation of kynurenine from tryptophan. J Biol Chem 229:889–896

12. Rothberg S, Hayaishi O (1957) Studies on oxygenases; enzymatic oxidation of imidazolacetic acid. J Biol Chem 229:897–903

13. Saito Y, Hayaishi O, Rothberg S (1957) Studies on oxygenases; enzymatic formation of 3-hydroxy-α-kynurenine from α-kynurenine. J Biol Chem 229:921–934

14. Dalgliesh CE, Knox WE, Neuberger A (1951) Intermediary metabolism of tryptophan. Nature 168:20–22

15. Knox WE, Mehler AH (1950) The conversion of tryptophan to kynurenine in liver. I. The coupled tryptophan peroxidase-oxidase system forming formylkynurenine. J Biol Chem 187:419–430

16. Tanaka T, Knox WE (1959) The nature and mechanism of the tryptophan pyrrole (peroxidase-oxidase) reaction of Pseudomonas and of rat liver. J Biol Chem 234:1162–1170

17. Yamamoto S, Hayaishi O (1967) Tryptophan pyrrole of rabbit intestine. α- and γ-tryptophan-cleaving enzyme or enzymes. J Biol Chem 242:5260–5266

18. Sono M, Roach MP, Coulter ED, Dawson JH (1996) Heme-containing oxygenases. Chem Rev 96:2841–2888

19. Hayaishi O, Stanier RY (1951) The bacterial oxidation of tryptophan. III. Enzymatic activities of cell-free extracts from bacteria employing the aromatic pathway. J Bacteriol 62:691–709

20. Maeno H, Feigelson P (1967) Spectral studies on the catalytic mechanism and activation of Pseudomonas tryptophan oxygenase (tryptophan pyrrole). J Biol Chem 242:596–601

21. Brady FO, Forman HJ, Feigelson P (1971) Role of superoxide and hydroperoxide in reductive activation of tryptophan-2,3-dioxygenase. J Biol Chem 246:7119

22. Brady FO (1975) Tryptophan 2,3-dioxygenase: a review of the roles of the heme and copper cofactors in catalysis. Bioinorg Chem 5:167–182

23. Ishimura Y, Nozaki M, Hayaishi O (1970) Oxygenated form of δ-tryptophan. 2,3-dioxygenase as reaction intermediate. J Biol Chem 245:3593

24. Hirata F, Hayaishi O, Tokuyama T, Seno S (1974) In vitro and in vivo formation of two new metabolites of melatonin. J Biol Chem 249:1311–1313

25. Hayaishi O (1975) Indoleamine 2,3-dioxygenase a new vista in tryptophan-metabolism. Acta Vitaminol Enzymol 29:17–20

26. Hayaishi O, Hirata F, Fujiwara M, Senoh S, Tokuyama T (1975) Indoleamine 2,3-dioxygenase. 2. Biological function. Acta Vitaminol Enzymol 29:291–293
27. Hirata F, Hayaishi O (1975) Studies on indoleamine 2,3-dioxygenase. 1. Superoxide anion as substrate. J Biol Chem 250:5960–5966
28. Hirata F, Nomiyama S, Hayaishi O (1975) Indoleamine 2,3-dioxygenase. 1. Catalytic and molecular-properties. Acta Vitaminol Enzymol 29:288–290
29. Hirata F, Ohnishi T, Hayaishi O (1977) Indoleamine 2,3-dioxygenase. characterization and properties of enzyme O-2-complex. J Biol Chem 252:4637–4642
30. Ohnishi T, Hirata F, Hayaishi O (1977) Indoleamine 2,3-dioxygenase—potassium superoxide as substrate. J Biol Chem 252:4643–4647
31. Fujiwara M, Shibata M, Watanabe Y, Nukiwa T, Hirata F, Mizuno N, Hayaishi O (1978) Indoleamine 2,3-dioxygenase—formation of l-kyurenine from l-tryptophan in cultured rabbit pineal-gland. J Biol Chem 253:6081–6085
32. Shimizu T, Nomiyama S, Hirata F, Hayaishi O (1978) Indoleamine 2,3-dioxygenase—purification and some properties. J Biol Chem 253:4700–4706
33. Taniguchi T, Sono M, Hirata F, Hayashi O, Tamura M, Hayashi K, Iizuka T, Ishimura Y (1979) Indoleamine 2,3-dioxygenase—kinetic studies on the binding of superoxide anion and molecular-oxygen to enzyme. J Biol Chem 254:3288–3294
34. Hayaishi O, Hirata F, Ohnishi T, Henry JP, Rosenthal I, Katoh A (1977) Indoleamine 2,3-dioxygenase—incorporation of (02)-0-18- and (02)-0-18 into reaction-products. J Biol Chem 252:3548–3550
35. Opitz CA, Lützenberger UM, Sahm F, Ott M, Trütscher L, Trump S, Schumacher T, Jestaedt L, Schrenk D, Weller M, Jugold M, Guillemin GI, Miller CL, Lutz C, Radlwimmer B, Lehmann I, von Deimling A, Wick W, Platten M (2011) An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. Nature 478:197–203
36. Knox WE (1952) Fed Proc 11:240
37. Ren S, Liu H, Licad E, Correia MA (1996) Expression of rat tryptophan dioxygenase. 1. Superoxide anion as substrate. J Biol Chem 271:2098–2103
38. Basran J, Rafice SA, Chauhan N, Efimov I, Cheesman MR, Batabyal D, Yeh SR (2007) Human tryptophan dioxygenase: a redox study of human tryptophan 2,3-dioxygenase. Int J Biochem Cell Biol 39:565–578
39. Batabyal D, Yeh SR (2007) Human tryptophan dioxygenase: resonance Raman spectroscopic analysis. J Biochem Tokyo 145:505–515
40. Fu R, Gupta R, Geng J, Dornevile K, Wang S, Zhang Y, Hendrich MP, Liu A (2011) Enzyme reactivation by hydrogen peroxide in heme-based tryptophan dioxygenase. J Biol Chem 286:26541–26554
41. Geng J, Dornevile K, Liu A (2012) Chemical rescue of the distal histidine mutants of tryptophan 2,3-dioxygenase. J Am Chem Soc 134:12209–12218
42. Rosell FJ, Kuo HH, Mauk AG (2011) NADH oxidase activity of indoleamine 2,3-dioxygenase. J Biol Chem 286:29273–29283
43. Feigelson P, Greengard O (1961) A microsomal iron-porphyrin activator of rat liver tryptophan pyrrolyase. J Biol Chem 236:153–157
44. Greengard O, Feigelson P (1961) The activation and induction of rat liver tryptophan pyrrolyse in vivo by its substrate. J Biol Chem 236:158–161
45. Feigelson P, Greengard O (1962) Regulation of liver tryptophan pyrrolyase activity. J Biol Chem 237:1908–1913
46. Poillon WN, Maeno H, Koike K, Feigelson P (1969) Tryptophan dioxygenase of Pseudomonas acidovorans. Purification, composition, and subunit structure. J Biol Chem 4:3347–3456
47. Brady FO, Monaco ME, Forman HJ, Schutz G, Feigelson P (1972) On the role of copper in activation of and catalysis by tryptophan-2,3-dioxygenase. J Biol Chem 247:7915–7922
48. Ishimura Y, Hayaishi O (1973) Noninvolvement of copper in t-tryptophan 2,3-dioxygenase reaction. J Biol Chem 248:8610–8612
49. Ishimura Y, Makino R, Ueno R, Sakaguchi K, Brady FO, Feigelson P, Aisen P, Hayaishi O (1980) Copper is not essential for the catalytic activity of t-tryptophan 2,3-dioxygenase. J Biol Chem 255:3835–3837
50. Papadopoulou ND, Mewies M, McLean KJ, Seward HE, Svisutlenko DA, Munro AW, Raven EL (2005) Redox and spectroscopic properties of human indoleamine 2,3-dioxygenase and a His303Ala variant: implications for catalysis. Biochemistry 44:14318–14328
51. Sugimoto H, Oda S, Otsuki T, Hino T, Yoshida T, Shiro Y (2006) Crystal structure of human indoleamine 2,3-dioxygenase: catalytic mechanism of O2 incorporation by a heme-containing dioxygenase. Proc Natl Acad Sci USA 103:2611–2616
52. Voltiero E, Mitchell DA, Page MJ, MacGillivray RTA, Sadowski IJ, Roberge M, Mauk AG (2006) Cytochrome b5 is a major reductant in vivo of human indoleamine 2,3-dioxygenase expressed in yeast. FEBS Lett 580:2205–2208
53. Littlejohn TK, Takikawa O, Skylas D, Jamie JF, Walker MJ, Truscott RJW (2000) Expression and purification of recombinant human indoleamine 2,3-dioxygenase. Protein Expr Purif 19:22–29
54. Austin CJ, Astelbauer F, Kosim-Satyaputra P, Ball H, Willows R, Jamie J, Hunt N (2009) Mouse and human indoleamine 2,3-dioxygenase display some distinct biochemical and structural properties. Amino Acids 36:99–106
55. Dick R, Murray BP, Reid MJ, Correia MA (2001) Structure-function relationships of rat hepatic tryptophan 2,3-dioxygenase: identification of the putative heme-ligating histidine residues. Arch Biochem Biophys 392:71–78
56. Manandhar SP, Shimada H, Nagano S, Egawa T, Ishimura Y (2002) Subunit structure of recombinant rat liver t-tryptophan 2,3-dioxygenase. Int Congr Ser 1233:161–169
57. Austin CJ, Mizrak D, Matin A, Sirijovski N, Kosim-Satyaputra P, Willows RD, Roberts TH, Truscott RJ, Polekhina G, Parker MW, Jamie JF (2004) Optimised expression and purification of recombinant human indoleamine 2,3-dioxygenase. Protein Expr Purif 37:392–398
58. Austin CJ, Kosim-Satyaputra P, Smith JR, Willows RD, Jamie JF (2013) Mutation of cysteine residues alters the heme-binding pocket of indoleamine 2,3-dioxygenase-1. Biochem Biophys Res Commun 436:595–600
59. Austin CJ, Mailu BM, Maghzal GJ, Sanchez-Perez A, Rahils S, Zocher K, Yuasa HJ, Arthur JW, Becker K, Stocker R, Hunt NH, Ball HJ (2010) Biochemical characteristics and inhibitor selectivity of mouse indoleamine 2,3-dioxygenase-2. Amino Acids 39:565–578
60. Fororuh F, Anderson JL, Mowat CG, Vorobiev SM, Hussain A, Abashidze M, Bruckmann C, Thackray SJ, Seetharaman J, Tucker T, Xiao R, Ma LC, Zhao L, Acton TB, Montelione GT, Chapman SK, Tong L (2007) Molecular insights into substrate recognition and catalysis of tryptophan 2,3-dioxygenase. Proc Natl Acad Sci USA 104:473–478
61. Zhang Y, Kang SA, Mukherjee T, Bale S, Crane BR, Begley TP, Ealick SE (2007) Crystal structure and mechanism of tryptophan 2,3-dioxygenase, a heme enzyme involved in tryptophan catabolism and in quinolinate biosynthesis. Biochemistry 46:145–155
63. Yuasa HJ, Ushigoe A, Ball HJ (2011) Molecular evolution of bacterial indoleamine 2,3-dioxygenase. Gene 485:22–31
64. Li JS, Han Q, Fang JM, Rizzi M, James AA, Li JY (2007) Biochemical mechanisms leading to tryptophan 2,3-dioxygenase activation. Arch Insect Biochem 64:74–87
65. Paglino A, Lombardo F, Arba R, Rizzi M, Rossi F (2008) Puriﬁcation and biochemical characterization of a recombinant Anopheles gambiae tryptophan 2,3-dioxygenase expressed in Escherichia coli. Insect Biochem Mol Biol 38:871–876
66. Huang W, Gong Z, Li J, Ding J (2013) Crystal structure of Drosophila melanogaster tryptophan 2,3-dioxygenase reveals insights into substrate recognition and catalytic mechanism. J Struct Biol 181:291–299
67. Yuasa HJ, Ball HJ (2011) Molecular evolution and characterization of fungal indoleamine 2,3-dioxygenases. J Mol Evol 72:160–168
68. Yuasa HJ, Ball HJ (2012) The evolution of three types of indoleamine 2,3 dioxygenases in fungi with distinct molecular and biochemical characteristics. Gene 504:64–74
69. Hu XL, Bao ZM, Hu JJ, Shao MY, Zhang LL, Bi K, Zhan AB, Mauk AG (2011) The renaissance of indoleamine 2,3 dioxygenases. Aquaculture 37:1187–1194
70. Mauk AG (2011) The renaissance of indoleamine 2,3-dioxygenase. Plenary lecture, ICBC meeting, Vancouver
71. Uyttenhove C, Pilotte L, Theate I, Stroobant V, Colan D, Parmenier N, Boon T, Van den Eynde BJ (2003) Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. Nat Med 9:1269–1274
72. Lob S, Konigsrainer A, Rammensee HG, Opelz G, Terness P (2009) Inhibitors of indoleamine-2,3-dioxygenase for cancer therapy: can we see the wood for the trees? Nat Rev Cancer 9:445–452
73. Chen W (2011) IDO: more than an enzyme. Nat Immunol 12:809–811
74. Efimov I, Basran J, Thackray SJ, Handa S, Mowat CG, Raven EL (2011) Structure and reaction mechanism in the heme dioxygenases. Biochemistry 50:2717–2724
75. Milledet ES, Efimov I, Basran J, Handa S, Mowat CG, Raven EL (2012) Heme-containing dioxygenases involved in tryptophan oxidation.Curr Opin Chem Biol 16:60–66
76. Geng J, Liu A (2014) Heme-dependent dioxygenases in tryptophan oxidation. Arch Biochem Biophys 544:18–26
77. Peng YH, Ueng SH, Tseng CT, Hung MS, Song JS, Wu JS, Liao FY, Fan YS, Wu MH, Hsiao WC, Hsieh CC, Lin SY, Cheng CY, Tu CH, Lee LC, MF Cheng, Shia KS, Shih C, Wu SY (2016) Important hydrogen bond networks in indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor design revealed by crystal structures of imidazoloeisoindeo derivatives with IDO1. J Med Chem 59:282–293
78. Tojo S, Kohno T, Tanaka T, Kamioka S, Ota Y, Ishii T, Kaminoto K, Asano S, Isobe Y (2014) Crystal structures and structure-activity relationships of imidazolothiazole derivatives as IDO1 inhibitors. ACS Med Chem Lett 5:1119–1123
79. Meng B, Wu D, Gu J, Ouyang S, Ding W, Liu ZJ (2014) Structural and functional analyses of human tryptophan 2,3-dioxygenase. Proteins 82:3210–3216
80. Wu JS, Lin SY, Liao FY, Hsiao WC, Lee LC, Peng YH, Hsieh CL, Wu MH, Song JS, Yueh A, Chen CH, Yeh SH, Liu CY, Lin SY, Yeh TK, Hsu JT, Shih C, Ueng SH, Hung MS, Wu SY (2015) Identiﬁcation of substituted naphthothiazoles as novel tryptophan 2,3-dioxygenase (TDO) inhibitors through structure-based virtual screening. J Med Chem 58:7807–7819
81. Gupta R, Fu R, Liu A, Hendrich MP (2010) EPR and Mossbauer spectroscopy show inequivalent hemes in tryptophan dioxygenase. J Am Chem Soc 132:1098–1109
82. Lewis-Ballester A, Forouhar F, Kim S-M, Lew S, Wang Y, Karkosh S, Seetharaman J, Batabal D, Chiang B-Y, Hussain M, Correia MA, Yeh S-R, Tong L (2016) Molecular basis for catalysis and substrate-mediated cellular stabilization of human tryptophan 2,3-dioxygenase. Sci Rep 6:35169. doi:10.1038/srep35169.
83. Alvarez L, Lewis-Ballester A, Roitberg A, Estrin DA, Yeh SR, Marti MA, Capece L (2016) Structural study of a ﬂexible active site loop in human indoleamine 2,3-dioxygenase and its functional implications. Biochemistry 55:2785–2793
84. Liou SH, Mahomed M, Lee YT, Goodin DB (2016) Eﬀector roles of putidaredoxin on cytochrome P450cam conformational states. J Am Chem Soc 138:10163–10172
85. Lee YT, Glazer EC, Wilson RF, Stout CD, Goodin DB (2011) Three clusters of conformational states in P450cam reveal a multistep pathway for closing of the substrate access channel. Biochemistry 50:693–703
86. Hollingsworth SA, Batabyal D, Nguyen BD, Poulos TL (2016) Conformational selectivity in cytochrome P450 redox partner interactions. Proc Natl Acad Sci USA 113:8723–8728
87. Hamilton GA (1969) Mechanisms of two- and four-electron oxidations catalyzed by some metalloenzymes. Adv Enzymol Relat Areas Mol Biol 32:55–96
88. Chauhan N, Thackray SJ, Raﬁce SA, Eaton G, Lee M, Efimov I, Basran J, Jenkins PR, Mowat CG, Chapman SK, Raven EL (2009) Reassessment of the reaction mechanism in the heme dioxygenases. J Am Chem Soc 131:4186
89. Aitken JB, Austin CJ, Hunt NH, Ball HJ, Lay PA (2014) The Fe-heme structure of met-indoleamine 2,3-dioxygenase-2 determined by X-ray absorption ﬁne structure. Biochem Biophys Res Commun 450:25–29
90. Chung LW, Li X, Sugimoto H, Shiro Y, Morokuma K (2008) Density functional theory study on a missing piece in understanding of heme chemistry: the reaction mechanism for indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase. J Am Chem Soc 130:12299–12309
91. Chung LW, Li X, Sugimoto H, Shiro Y, Morokuma K (2010) ONIOM study on a missing piece in our understanding of heme chemistry: bacterial tryptophan 2,3-dioxygenase with dual oxi- dants. J Am Chem Soc 132:11993–12005
92. Capece L, Lewis-Ballester A, Batabal D, Di Russo N, Yeh SR, Estrin DA, Marti MA (2010) The first step of the dioxygenation reaction carried out by tryptophan dioxygenase and indoleamine 2,3-dioxygenase as revealed by quantum mechanical/molecular mechanical studies. J Biol Inorg Chem 15:811–823
93. Capece L, Lewis-Ballester A, Yeh SR, Estrin DA, Marti MA (2012) Complete reaction mechanism of indoleamine 2,3-dioxygenase as revealed by QM/MM simulations. J Phys Chem B 116:1401–1413
94. Lu C, Lin Y, Yeh SR (2009) Inhibitory substrate binding site of human indoleamine 2,3-dioxygenase. J Am Chem Soc 131:12866–12867
95. Chauhan N, Thackray SJ, Raﬁce SA, Eaton G, Lee M, Efimov I, Basran J, Jenkins PR, Mowat CG, Chapman SK, Raven EL (2009) Reassessment of the reaction mechanism in the heme dioxygenases. J Am Chem Soc 131:4186–4187
96. Thackray SJ, Bruckmann C, Anderson JL, Campbell LP, Xiao R, Zhao L, Mowat CG, Forouhar F, Tong L, Chapman SK (2008) Histidine 55 of tryptophan 2,3-dioxygenase is not an active site base but regulates catalysis by controlling substrate binding. Biochemistry 47:10677–10684
97. Lewis-Ballester A, Batabyal D, Egawa T, Lu C, Lin Y, Marti MA, Capece L, Estrin DA, Yeh SR (2009) Evidence for a ferryl intermediate in a heme-based dioxygenase. Proc Natl Acad Sci USA 106:17371–17376
98. Makino R, Obayashi E, Hori H, Iizuka T, Mashima K, Shiro Y, Ishimura Y (2015) Initial O(2) insertion step of the tryptophan
dioxygenase reaction proposed by a heme-modification study. Biochemistry 54:3604–3616
99. Makino R, Izuka T, Sakaguchi K, Ishimura Y (1983) Effects of substitution on the activity of heme-containing oxygenases. Oxygenases and oxygen metabolism (a symposium in honor of Osamu Hayaishi). Academic Press, New York, pp 468–477
100. Basran J, Efimov I, Chauhan N, Thackray SJ, Krupa JL, Eaton G, Griffith GA, Mowat CG, Handa S, Raven EL (2011) The mechanism of formation of N-formylkynurenine by heme dioxygenases. J Am Chem Soc 133:16251–16257
101. Yanagisawa S, Yotsuya K, Hashiwaki Y, Horitani M, Sugimoto H, Shiro Y, Appelman EH, Ogura T (2010) Identification of the Fe–O2 and the Fe=O heme species for indoleamine 2,3-dioxygenase during catalytic turnover. Chem Lett 39:36–37
102. Booth ES, Basran J, Lee M, Handa S, Raven EL (2015) Substrate oxidation by indoleamine 2,3-dioxygenase. J Biol Chem 290:30924–30930
103. Efimov I, Basran J, Thackray SJ, Handa S, Mowat CG, Raven EL (2012) Heme-Containing Dioxygenases. In: van Eldik R (ed) Advances in inorganic chemistry. Academic Press, London, pp 34–51
104. Sono M, Taniguchi T, Watanabe Y, Hayaishi O (1980) Indoleamine 2,3-dioxygenase—equilibrium studies of the tryptophan binding to the ferric, ferrous, and co-bound enzymes. J Biol Chem 255:1339–1345
105. Chauhan N, Basran J, Efimov I, Svistunenko DA, Seward HE, Moody PC, Raven EL (2008) The role of serine 167 in human indoleamine 2,3-dioxygenase: a comparison with tryptophan 2,3-dioxygenase. Biochemistry 47:4761–4769
106. Efimov I, Basran J, Sun X, Chauhan N, Chapman SK, Mowat CG, Raven EL (2012) The mechanism of substrate inhibition in human indoleamine 2,3-dioxygenase. J Am Chem Soc 134:3034–3041
107. Kolawole AO, Hixon BP, Dameron LS, Chrisman IM, Smirnov VV (2015) Catalytic activity of human indoleamine 2,3-dioxygenase (hIDO1) at low oxygen. Arch Biochem Biophys 570:47–57
108. Weber B, Nickel E, Horn M, Nienhaus K, Nienhaus GU (2014) Substrate inhibition in human indoleamine 2,3-dioxygenase. J Phys Chem Lett 5:756–761
109. Macchiarulo A, Nuti R, Bellocci D, Camaioni E, Pellicciai R (2007) Molecular docking and spatial coarse graining simulations as tools to investigate substrate recognition, enhancer binding and conformational transitions in indoleamine-2,3-dioxygenase (IDO). Biochim Biophys Acta 1774:1058–1068
110. Capece L, Arrar M, Roitberg AE, Yeh SR, Marti MA, Estrin DA (2010) Substrate stereo-specificity in tryptophan dioxygenase and indoleamine 2,3-dioxygenase. Proteins 78:2961–2972
111. Nickel E, Nienhaus K, Lu C, Yeh SR, Nienhaus GU (2009) Ligand and substrate migration in human indoleamine 2,3-dioxygenase. J Biol Chem 284:31548–31554
112. Yuasa HJ (2016) High L-Trp affinity of indoleamine 2,3-dioxygenase 1 is attributed to two residues located in the distal heme pocket. FEBS Lett. doi:10.1111/febs.13834
113. (2016) Nature Digest (Japanese edition) 13:26–31
114. Raven E, Dunford HB (2015) Heme peroxidases. Royal Society of Chemistry, Cambridge
115. Ortiz de Montellano PR (1995) Cytochrome P450: structure, mechanism, and biochemistry. Plenum Press, New York
116. Ortiz de Montellano PR (2005) Cytochrome P450: structure, mechanism, and biochemistry, 3rd edn. Kluwer Academic/Plenum Publishers, Dordrecht
117. Basran J, Booth ES, Lee M, Handa S, Raven EL (2016) Analysis of reaction intermediates in Tryptophan 2,3-Dioxygenase: a comparison with Indoleamine 2,3-Dioxygenase. Biochemistry. doi:10.1021/acs.biochem.6b01005
118. Kuo HH, Mauk AG (2012) Indole peroxidase activity of indoleamine 2,3-dioxygenase. Proc Natl Acad Sci USA 109:13966–13971