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Chemical Biology

Structure and Function of Human Tyrosinase and Tyrosinase-Related Proteins

Xuelei Lai,[a, b] Harry J. Wichers,[c] Montserrat Soler-Lopez,*[b] and Bauke W. Dijkstra*[^a]


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Abstract: Melanin is the main pigment responsible for the color of human skin, hair and eye. Its biosynthesis requires three melanogenic enzymes, tyrosinase (TYR), and the tyrosinase-related proteins TYRP1 and TYRP2. The difficulty of isolating pure and homogeneous proteins from endogenous sources has hampered their study, and resulted in many contradictory findings regarding their physiological functions. In this review, we summarize recent advances on the structure and function of TYR and TYRPs by virtue of the crystal structure of human TYRP1, which is the first available structure of a mammalian melanogenic enzyme. This structure, combined with tyrosinase structures from other lower eukaryotes and mutagenesis studies of key active site residues, sheds light on the mechanism of TYR and TYRPs. Furthermore, a TYRP1-based homology model of TYR provides a high-quality platform to map and analyze albinism-related mutations, as well as the design of specific antimelanogenic compounds. Finally, we provide perspectives for future structure/function studies of TYR and TYRPs.

1. Introduction

Tyrosinases (also called monophenol monoxygenases, EC 1.14.18.1) are type 3 copper proteins with two copper ions in the active site. They catalyze the conversion of monophenols (e.g., tyrosine) into o-diphenols (monophenolase activity), followed by the oxidation of the o-diphenols to the corresponding o-quinone derivatives (diphenolase activity; Figure 1). The related catechol oxidases only catalyze the second reaction, using o-diphenols as substrates.

![Figure 1. Reaction catalyzed by tyrosinase.](image)

Starting from tyrosine, the final product of the tyrosinase-catalyzed reaction is dopaquinone, which is a precursor of melanin. Melanins are pigments that are widespread in organisms ranging from bacteria, fungi, plants, to mammals. In mammals, melanin is present in many organs, such as eye, ear, brain, and skin. In the latter organ, melanin gives protection against DNA damage induced by the UV radiation of the sun. The relative amount of melanin is a key determinant of color-based ethnic diversification in humans.

In humans, melanin is synthesized in melanosomes, which are organelles inside specialized cells such as melanocytes in skin and hair, and retinal pigment epithelium cells in the eye. Three tyrosinase-like enzymes take part in its biosynthesis, tyrosinase (TYR) and tyrosinase-related proteins 1 and 2 (TYRP1 and TYRP2). All three melanogenic enzymes are metal-containing glycoproteins and have a single transmembrane α-helix. They share roughly 40% amino acid sequence identity and around 70% similarity (Figure 2). Mutations in the TYR or TYRP1 genes cause oculocutaneous albinism (OCA1 and OCA3, respectively), a group of autosomal recessive disorders characterized by reduced production of melanin in skin, hair and eyes. In addition, TYR and TYRP1 variants are significantly associated with risk of melanoma, a malignant tumor of melanocytes that causes the majority of deaths related to skin cancer. On the other hand, excess melanin production or abnormal distribution can cause pigmentation disorders, such as over-tanning, age spots and melasma, which has prompted the development of skin-whitening compounds to reduce the melanin content. Furthermore, inhibition of melanin synthesis is being considered as a valid therapeutic strategy for the treatment of advanced melanotic melanomas.

In this Minireview, we focus on the structure and function of human TYR and TYRPs based on recent advances. Studies of tyrosinases from lower organisms have been extensively reviewed elsewhere. We have also generated models of TYR and TYRP2 in view of their high homology with TYRP1, based on which we discuss their catalytic function/mechanism and analyze the molecular basis of OCA1-related mutations. Finally, we discuss perspectives for antimelanogenic compound design.

2. Overall Architecture of TYR and TYRPs

TYR and TYRPs have four conserved regions, an N-terminal signal peptide, a large intra-melanosomal domain, a single transmembrane α-helix, and a small, flexible C-terminal cytoplasmic domain (Figure 3). The intra-melanosomal domain contains a cysteine (Cys)-rich subdomain and a catalytic tyrosinase-like subdomain with two metal-ion-binding sites (Figure 3a). The transmembrane domain anchors the protein to the inside of the melanosomal membrane. The cytoplasmic domain harbors a melanosomal sorting signal that diverts the protein to the melanosomal membrane.
TYRP1 has six sites (at Asn 96, 111, 161, 230, 290, 337, 371), which are important for maturation of the proteins. TYR contains seven N-glycosylation motifs (at Asn 86, 111, 161, 230, 290, 337, 371), which prompted the use of the enzyme as a model substrate to study the maturation of glycoproteins in the mammalian secretory pathway because of the visual nature of its enzymatic activity (melanin production). TYRP1 has six sites (at Asn 96, 104, 181, 304, 350, 385), all of which are glycosylated in the tested in vitro conditions, suggesting that the presence of the single transmembrane helix and/or cytosolic tail domain may be needed for complex formation. Analysis of the association behavior of full-length proteins may settle this issue. Another hypothesis is that the cysteine residues in the Cys-rich subdomain assist in the incorporation of metal ions in the active site, as has been reported for cysteines in other tyrosinases. This is unlikely for TYRP1, since all cysteines in the subdomain are involved in disulfide bonds. Site-directed mutagenesis combined with metal content analysis of the resulting enzyme variants may shed further light on the role of the cysteine residues in metal ion incorporation.

The human melanogenic enzymes contain six or seven putative N-glycosylation sites (Figure 2), which are important for maturation of the proteins. TYR contains seven N-glycosylation motifs (at Asn 86, 111, 161, 230, 290, 337, 371), which prompted the use of the enzyme as a model substrate to study the maturation of glycoproteins in the mammalian secretory pathway because of the visual nature of its enzymatic activity (melanin production). TYRP1 has six sites (at Asn 96, 104, 181, 304, 350, 385), all of which are glycosylated in the

**Xuelei Lai**

Xuelei Lai did his PhD research at the European Synchrotron Radiation Facility, Grenoble, France, where he performed structural and biochemical studies on human tyrosinase and tyrosinase-related protein 1. He was awarded a PhD degree from the University of Groningen, the Netherlands, in 2017. He did a one-year postdoc research project at the University of Cambridge, UK, where he combined structural biology and genome-wide approaches to understand temperature perception mechanisms in plants. Currently, he is a postdoctoral researcher at the CEA, Grenoble, focusing on gene expression regulation and chromatin remodelling during floral development using combinatorial approaches of structural biology, proteomics, and next-generation sequencing.

**Prof. Dr. Harry Wichers**

Prof. Dr. Harry Wichers is biochemist by training, with immunology as a minor subject. He obtained his PhD degree from the University of Groningen, on the subject “Biotecnologische produktion of pharmaceuticals via cultured plant cells”. After working for 5 years for the Dutch Organisation for Applied Research (TNO) at its Biotechnology Department, he moved in 1990 to Wageningen Food and Biobased Research. He was involved in research on the biochemical characterization of quality-related parameters that determine food quality (taste, texture, and notably colour) (enzymatic browning catalyzed by polyphenol oxidases, aka tyrosinases). Currently, Harry Wichers is working on the relationship between food and its components and the immune system. Since April 2005, Harry Wichers is holder of the chair ‘Immunomodulation by Food’ at Wageningen University.

**Montserrat Soler-López**

Montserrat Soler-López obtained her PhD degree in structural biology of DNA from the Polytechnic University of Catalonia, in 2000. During her postdoctoral research at the EMBL in Grenoble (France) she worked on the structure determination of proteins involved in transcriptional regulation and nuclear transport. In 2005, she joined a structure-based drug discovery biotechnology company, Cystar Pharmaceuticals, as head of the structural biology unit and parallelizing processes as cloning and expression of therapeutic targets. In 2008 she was recruited as director of the Experimental Bioinformatics Lab (EBL), a joint initiative of the Barcelona Institute of Research in Biomedicine (IRB Barcelona) and the Barcelona Supercomputing Center (BSC), where she led the effort to integrate experimental biology data into computation-based predictions from diverse areas of systems and network biology, in particular genome-wide nucleosome positioning and ‘omics’ technologies to characterize protein interaction networks associated with complex diseases. Since 2014, she is a scientist and laboratory manager in the Structural Biology Group of the European Synchrotron Radiation Facility (ESRF). Her research interest is focused on melanogenic mechanisms of tyrosinases and mitochondrial bioenergetics in neurodegeneration.

**Bauke Dijkstra**

Bauke Dijkstra obtained his PhD degree in structural biology at the University of Groningen in 1980. After postdoctoral fellowships at the University of Utrecht, the Netherlands, and the University of California at Los Angeles, USA, he returned to the University of Groningen in 1985, first as associate professor, and from 1993 as full professor of Biophysical Chemistry with special interest in structural biology. From 2012–2014 he served as Director of Research for Life Sciences, Chemistry and Soft Matter Science at the European Synchrotron Radiation Facility in Grenoble, France. At present, he is emeritus professor of Biophysical Chemistry at the University of Groningen, the Netherlands.
crystal structure with various lengths of carbohydrate chains (Figures 2 and 3). However, we cannot exclude the possibility that glycosylation of TYRP1 in melanosomes differs from protein produced in insect cells, which may have functional consequences. TYRP2 also contains six N-glycosylation motifs (at Asn170, 178, 237, 300, 342, 377), of which four are equivalent to the TYRP1 sites. Only the N-glycosylation motifs at N304 and N385 (TYRP1 numbering) occur in all three melanogenic proteins. TYR has unique motifs at N111, N230, and N337 (equivalent to TYRP1 A121, S243, T352, respectively). The N-glycosylation motifs are thus not fully conserved among the three melanogenic proteins (Figure 2). The importance of the various glycosylation sites for the functioning of the enzymes is a subject for further study, as is the pattern and degree of glycosylation occurring inside the melanosomes.

3. Physiological Activity and Function of TYR and TYRPs

TYR, TYRP1 and TYRP2 are the only three proteins that are required for melanin biosynthesis (Figure 4), but their functions and activities are still not fully understood.

3.1. TYR

TYR is the only human melanogenic enzyme with well-established in vivo catalytic activity, although its precise catalytic mechanism is still under debate. In particular, the detailed interaction of substrates with the two active site copper ions, and the way how monophenolic substrates are activated, are important subjects of investigation. Unfortunately, no crystal structure with various lengths of carbohydrate chains (Figures 2 and 3). However, we cannot exclude the possibility that glycosylation of TYRP1 in melanosomes differs from protein produced in insect cells, which may have functional consequences. TYRP2 also contains six N-glycosylation motifs (at Asn170, 178, 237, 300, 342, 377), of which four are equivalent to the TYRP1 sites. Only the N-glycosylation motifs at N304 and N385 (TYRP1 numbering) occur in all three melanogenic proteins. TYR has unique motifs at N111, N230, and N337 (equivalent to TYRP1 A121, S243, T352, respectively). The N-glycosylation motifs are thus not fully conserved among the three melanogenic proteins (Figure 2). The importance of the various glycosylation sites for the functioning of the enzymes is a subject for further study, as is the pattern and degree of glycosylation occurring inside the melanosomes.

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structure of human TYR is available, but on the basis of the TYRP1 crystal structure, a good model of TYR could be generated (Figure 3b). Assuming that substrate binding is equivalent in TYR and TYRP1, the model suggests that their \( p \)-hydroxyl group interacts with the bridging water molecule between the two metal ions and with a serine residue (S394 in TYRP1, S380 in TYR) that is not present in tyrosinases from lower organisms. Interestingly, the S380P mutation has been associated with OCA1, suggesting a role for S380 in TYR activity. Indeed, the S380P and S380A TYR mutants showed a dramatic decrease in hydroxylase and oxidase activity, with the S380P mutation almost completely abolishing hydroxylase activity (Figure 5). Thus, although the precise role of S380 is unclear, this result highlights that S380 may be involved in substrate activation, and that differences between mammalian tyrosinases and those from lower organisms may significantly affect enzyme activity.

It is generally believed that monophenolic substrates are bound as phenolate ions following deprotonation of the hydroxyl group. Several residues have been proposed to assist in deprotonation, such as a conserved glutamate residue near CuA, or a water molecule activated by the same glutamate together with a nearby conserved asparagine residue (Figure 5c). The Glu and Asn are also present in TYR, but they have no direct interaction with the substrate’s hydroxyl group (Figure 5c). Their mutation into glycines (E345G, N364G) strongly reduced TYR’s hydroxylase activity, but the effect on the oxidase activity (for which no proton abstraction is needed) is much less. Thus, an indirect contribution to proton abstraction via water molecules in the active site seems possible. Further structural studies with substrate analogues are needed to pinpoint the structural details of the deprotonation.

### 3.2. TYRP1

The catalytic activity of TYRP1 is enigmatic. The mouse enzyme exhibits both tyrosine hydroxylase and \( \eta \)-DOPA oxidase activities. In addition, it appears to function as a dopachrome
In contrast, human TYRP1 seems to display only tyrosine hydroxylase activity and not DHICA oxidase activity. Intriguingly, purified, recombinant intra-melanosomal human TYRP1 produced in insect cells does not exhibit hydroxylase nor oxidase activities, in agreement with the crystal structure containing two redox-inactive zinc ions in the active site instead of copper. Producing recombinant TYR and TYRP1 under identical cell culture conditions without adding external sources of zinc or copper ions resulted consistently in TYR containing copper and TYRP1 containing zinc ions. Nevertheless, DHICA oxidase and low tyrosine hydroxylase activity can be conferred to TYRP1 when zinc is replaced by copper. Whether in vivo TYRP1 can also incorporate copper ions is not known. Which factors determine whether zinc or copper ions are incorporated in the native human melanogenic enzymes remains unclear. Interestingly, TYRP2 also contains zinc ions in the active site and displays dopachrome tautomerase activity. However, dopachrome tautomerase activity has not yet been confirmed or disproved for TYRP1. It cannot even be ruled out that this latter reaction can occur without enzyme.

Interestingly, TYRP1 binds typical tyrosinase substrates and inhibitors (tyrosine, mimosine, kojic acid, and tropolone), as shown by crystal structures. The binding of these compounds occurs by aromatic stacking interactions with H381 (TYRP1 numbering), ligation of their keto- and hydroxy groups to the zinc ions, and hydrogen-bonding interactions with S394 (TYRP1 numbering). However, recognition of the substrate's carboxylate group and interaction with any "substrate-guiding residues" in the second shell of the active site appear not to be essential. Thus, although TYRP1 can bind typical melanin biosynthesis analogues, the catalytic function of TYRP1 in the pathway is still a mystery. Still, its role in melanin synthesis is undisputed, given the incidence of OCA3-related mutations in the TYRP1 gene.
3.3. TYRP2

In the early 1990s it was reported that TYRP2 contains two zinc ions in the active site and isomerizes dopachrome to DHICA (5,6-dihydroxy-indole-2-carboxylic acid; see Figure 4). Based on the similarity of TYRP2 to tyrosinases, dopachrome was proposed to bind to the zinc ions in a bidentate way, with its two hydroxyl groups binding to different zinc ions, each displacing a water molecule. An electronic rearrangement in the indole ring then leads to the formation of DHICA as the product (Figure 4). Two features of this hypothesis differ from what is observed for TYRP1. Firstly, it is assumed that two water molecules are displaced, while in TYRP1 only one water molecule or hydroxyl ion is coordinated by the two zinc ions. Secondly, it is assumed that the substrate binds in a bidentate mode, while in the TYRP1 structures the substrate/inhibitors are only bound to ZnA. However, we cannot exclude that the presence of an indole core in dopachrome instead of a phenyl core in tyrosine/L-DOPA results in a different substrate-binding mode in the active site of TYRP2; this may be verified by a 3D structure of TYRP2 with bound substrate.

Difficulty in obtaining sufficient amounts of pure protein from natural sources has been the major bottleneck for structural and mechanistic studies of TYRP2. Recent successful production and purification of fully glycosylated and active TYR and TYRP1 recombinant proteins may provide a good starting point for TYRP2 recombinant production. Purified protein could enable crystallographic as well as enzyme kinetics studies, which would eventually shed light on the nature of its active site and catalytic mechanism.

4. Analysis of OCA-Related Mutations

The 3D model of TYR (Figure 3b) provides a useful tool for the mapping and structural analysis of OCA-related mutations. According to the Human Gene Mutation Database, 249 missense/nonsense mutations in TYR are associated with OCA1, affecting 177 unique amino acids, of which 169 are part of the current model. Interestingly, out of the 96 residues in the Cys-rich subdomain (residues 19–114), more than one third (i.e. 36 residues) have been implicated in OCA1, supporting the importance of this domain in mammalian tyrosinases. In particular, 8 out of the 10 disulfide bond-forming cysteines (C24, C35, C36, C46, C55, C89, C91 and C100) are associated with OCA1 (Figure 6). Other mutations in this subdomain are irregularly distributed, which may indicate the general importance of the domain for the overall folding, and/or maturation or processing of the protein in vivo.

Not surprisingly, all six copper-coordinating histidines are among the severely pathological mutations (Figure 6). Although only H211 has been assigned to OCA1A, a subtype of OCA1 with patients suffering from life-long absence of melanin, our model suggests that also the other five histidines (H180, H202, H363, H367 and H390; Figure 6) would result in OCA1A, since they are critical copper ligands in the active site, and their substitution would yield an inactive enzyme.

A subset of OCA1 related mutations, including R402Q, P406L, and R422Q, causes temperature-sensitive oculocutaneous albinism (OCA1-TS), due to a temperature-sensitive form of TYR with optimal tyrosinase activity at temperatures below 37 °C. As a result, pigmentation is generally more prominent in the extremities (ears, face and legs), where the temperature is lower than in other parts of the body. In the TYR model (Figure 6) R402 is surface-exposed and forms a hydrogen bond with Q399. An R402Q mutation may weaken this interaction, causing TYR to (partially) unfold at higher temperatures, but not at lower temperatures. Similarly, the surface-located R422 has a hydrogen-bonding interaction with the carbonyl oxygen of Y411. Although a similar interaction can be made by the R422Q mutant, the removal of the positive charge may weaken the interaction and reduce the stability of the enzyme, explaining the temperature-sensitive behavior of the mutant protein. Finally, P406 in a surface loop likely rigidifies the main chain conformation and thereby stabilizes the loop. Replacing Pro by a hydrophobic Leu would not only introduce more flexibility, but also expose a hydrophobic side chain to the solvent. Both factors may contribute to lowering the thermal stability of TYR.

5. Design of Antimelanogenic Compounds

Compounds that inhibit the melanogenic enzymes to reduce melanin production in human skin are highly sought for in the cosmetic industry. In addition, such compounds are also promising as adjuvant drugs for treating melanoma. TYR is the initiating and rate-limiting enzyme in the melanin biosynthesis pathway, and therefore the prime target for the design.
of antimelanogenic compounds. However, difficulties with obtaining pure human TYR and the absence of a crystal structure have impeded progress. Therefore, in the last decades, most tyrosinase inhibitors were developed using mushroom tyrosinase as a model enzyme, and by computational docking using bacterial and mushroom tyrosinase crystal structures. First crystal structures of human TYRP1, and a structural model of human TYR generated from it, now provide a much-awaited, much better platform for structure-based design of antimelanogenic compounds.

The crystal structures of TYRP1 with various bound ligands have already revealed that Y362, R374, H381, S394, and T391 (TYRP1 numbering) are key residues for ligand binding, providing a good starting point for drug design. In addition, for chelator-like inhibitors such as tropolone, the two zinc ions are also essential binding partners. Compared to TYRP1, the active site of TYR (as mimicked by the TYRP1-3M structure) is somewhat more hydrophobic, but the ligand coordination patterns in the active site are nearly identical. However, it should be noted that TYR is a redox enzyme with two copper ions rather than zinc ions in the active site, which may cause the ligands to bind differently from the way they are bound in TYRP1. Experimental verification of the ligand binding mode in Cu-substituted TYRP1 may give clues, if no TYR crystals of sufficient quality can be obtained.

Finally, the "second shell residues" in the active site, which are located at around 5.5–16 Å from the copper ions, are considered to control the enzyme's specificity and activity. Although the structures suggest that the second shell residues of TYRP1, and presumably of TYR as well, do not directly interact with substrates, they may affect the activity and dynamics of the proteins. Therefore, they may also need to be taken into account for the design of the compounds.

6. Summary and Outlook

TYR and TYRPs are key enzymes involved in melanin synthesis in humans. Their functional studies commenced in the early 1990s when their coding genes were cloned, but progress was relatively slow, and several findings were contradictory. TYR is the only melanogenic enzyme with a well-defined catalytic activity; the physiological functions of TYRP1 and TYRP2 are yet to be confirmed, although the enzymes are clearly important for melanin synthesis. An important breakthrough was the successful, high-yield recombinant production of TYR and TYRP1, allowing crystallization studies, and structure determination of TYRP1. Subsequent structural and activity studies of TYRP1 revealed that TYRP1 is a type 3 zinc protein, which refuted the long-time hypothesis of its oxidase function. The crystal structure of TYRP1 is also an excellent reference for modeling mammalian tyrosinases and related proteins because of their 40–50% sequence identity. Such models can help to understand OCA-related mutations, and facilitate the design of antimelanogenic compounds. However, despite the success of computational approaches, experimental validation of inhibitor binding modes will remain necessary, for which high-quality, well-diffracting TYR crystals are indispensable. Unfortunately, growing diffraction-quality crystals of TYR is still a major hurdle, in view of the high degree of N-linked glycosylation of TYR, TYRP1, and TYRP2. In this regard, generating variants with fewer N-glycosylation motifs may be a productive approach. Alternatively, considering that the full-length melanogenic proteins have been reported to form large hetero-dimer or hetero-trimer complexes in vivo, reconstitution of such complexes in vitro may enable their characterization by cryo-electron microscopy. This may give valuable information on the details of complex formation and its benefits in a biological context. Finally, the recombinant production of human TYR and TYRP1 may also enable high-throughput screening of potential inhibitors, which may considerably boost the field.

Conflict of interest

The authors declare no conflict of interest.

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