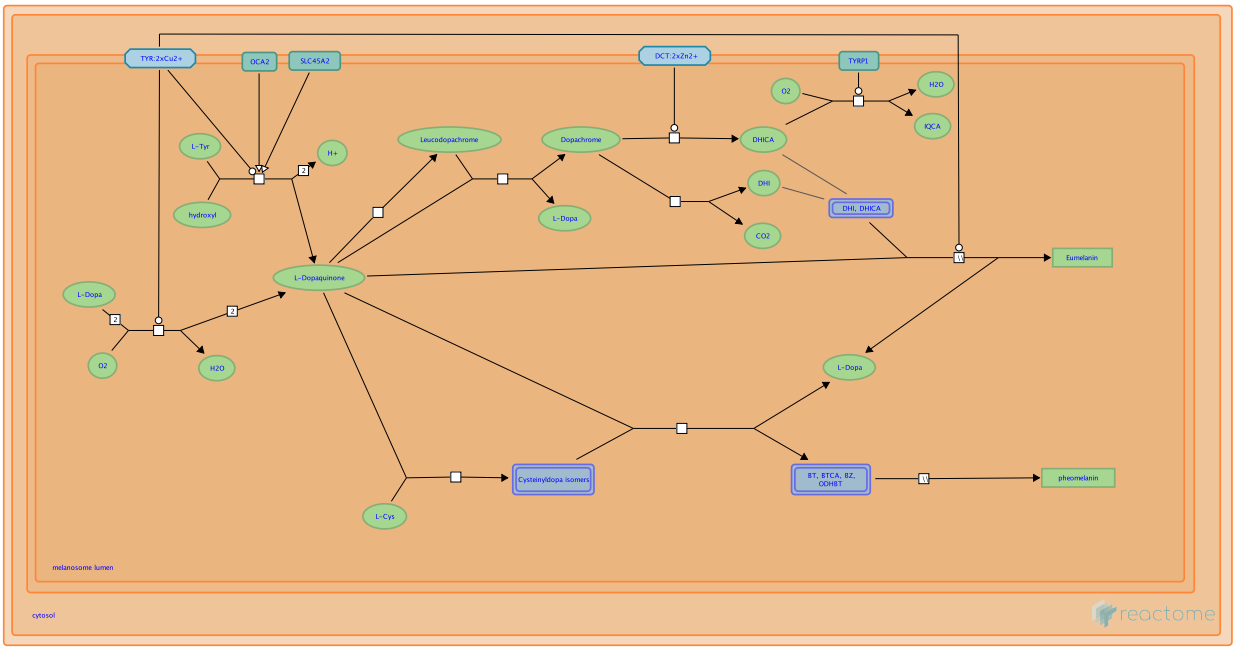
Melanin biosynthesis



D'Eustachio, P., Ito, S., Jassal, B., Jupe, S., d'Ischia, M.

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15/09/2021

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

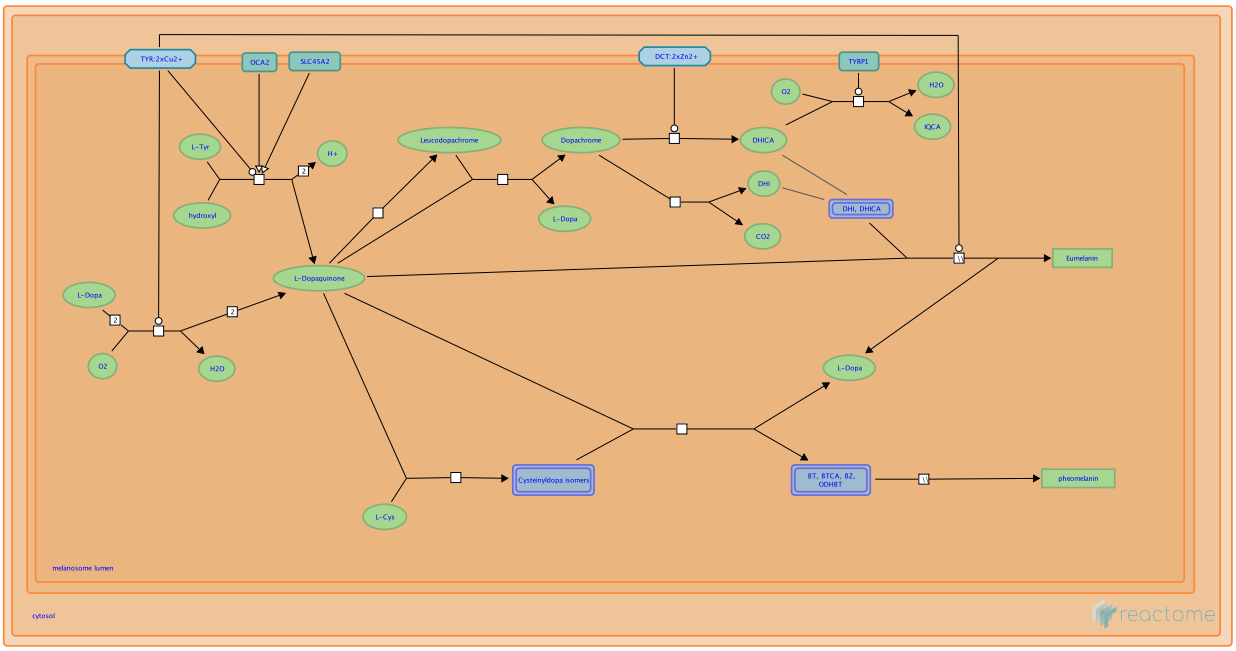
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Melanin biosynthesis ↗

Stable identifier: R-HSA-5662702



Melanin biosynthesis takes place in specialized cells called melanocytes, within membrane-bound organelles referred to as melanosomes. Melanosomes are transferred via dendrites to surrounding keratinocytes. Keratinocytes and melanocytes are collectively known as 'the epidermal melanin unit'. Each melanocyte is in contact with approximately 40 keratinocytes in the basal and suprabasal layers (Cichorek et al. 2013). Melanocytes are distributed in the epidermis, hair follicles, the inner ear and the eye (Yamaguchi et al. 2007, Tolleson 2005).

Melanocytes in mammals and birds produce two chemically distinct types of melanin, black to brown eumelanin and yellow to reddish-brown pheomelanin (Ito & Wakamatsu 2008, Simon et al. 2009, d'Ischia et al. 2013). These differ in their responses to UV radiation; eumelanin has the ability to convert absorbed light energy into heat energy (Meredith & Riesz 2004) and to detoxify reactive oxygen species (ROS) (Bustamante et al. 1993), while pheomelanin is a phototoxic pro-oxidant (Samokhvalov 2005). Most natural melanin pigments contain eumelanin and pheomelanin (Ito & Wakamatsu 2003) and are termed 'mixed' melanins. Neuromelanins are mixed melanin-like pigments which are mainly found in neurons of the substantia nigra and locus coeruleus (Fedorow et al. 2005). Synthesis of NM may prevent the accumulation of toxic catechol derivatives (Zecca et al. 2003). NM can sequester a variety of potentially damaging molecules such as beta-carbolines, heavy metal ions and 1-methyl-4-phenylpyridinium (MPP+) (D'Amato et al. 1986), a drug which causes Parkinson's Disease-like symptoms. Models suggest that mixed melanogenesis occurs in three stages (Ito et al. 2000). The initial stage of melanin biosynthesis is the production of cysteinyldopas, which continues while sufficient cysteine is available. The second stage is the oxidation of cysteinyldopas to produce pheomelanin, which continues while cysteinyldopa concentration is sufficiently high. The last stage is the production of eumelanin, which begins when cysteinyldopas and cysteine are depleted. The ratio of eumelanin to pheomelanin is determined by tyrosinase activity and the availability of tyrosine and cysteine (Land et al. 2003).

Literature references

Ito, S., Wakamatsu, K. (2008). Chemistry of mixed melanogenesis--pivotal roles of dopaquinone. *Photochem. Photobiol., 84*, 582-92. ↗

d'Ischia, M., Wakamatsu, K., Napolitano, A., Briganti, S., Garcia-Borron, JC., Kovacs, D. et al. (2013). Melanins and melanogenesis: methods, standards, protocols. *Pigment Cell Melanoma Res, 26*, 616-33. ↗

Editions

2015-01-13	Authored	Jupe, S.
2015-02-10	Edited	Jupe, S.
2015-02-13	Reviewed	Ito, S., d'Ischia, M.

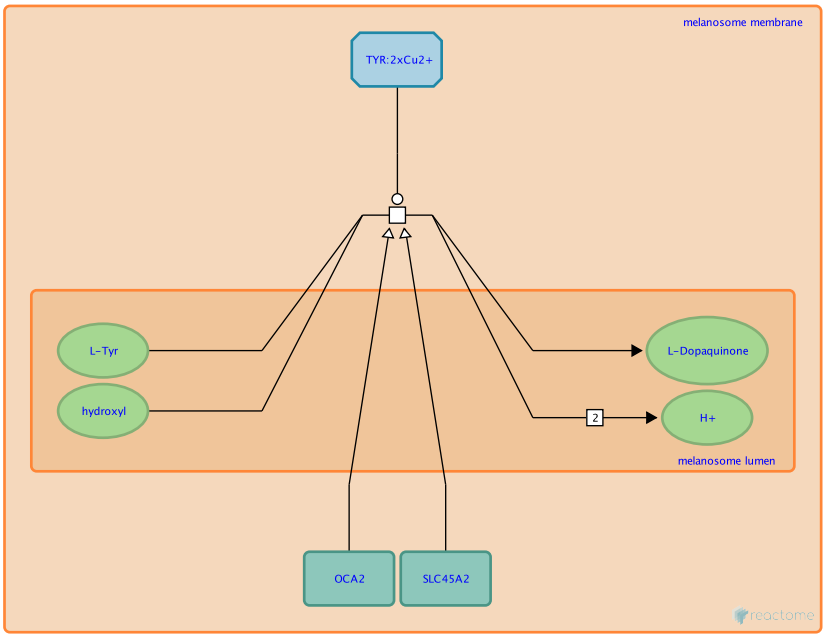
Tyrosinase oxidises tyrosine to dopaquinone ↗

Location: Melanin biosynthesis

Stable identifier: R-HSA-5662662

Type: transition

Compartments: melanosome membrane, melanosome lumen



Melanogenesis is initiated with the first step of tyrosine oxidation to dopaquinone, catalyzed by tyrosinase (Mason 1948, Hearing et al. 1980). This first step is the rate-limiting step in melanin synthesis; the remainder of the reaction sequence can proceed spontaneously at a physiological pH value (Halaban et al. 2002, Land et al. 2003).

The melanocyte-specific transporter protein (OCA2, aka P protein, pink-eyed dilution protein homolog) is postulated to play a role in the processing and intracellular trafficking of tyrosinase (TYR) in the melanosome (Potterf et al. 1998, Toyofuku et al. 2002). It is a 110-kDa integral melanosomal protein with 12 predicted transmembrane domains, suggesting a transport function but its exact physiological role is still unknown. In humans, mutations in the OCA2 gene result in oculocutaneous albinism type 2, a disorder of pigmentation characterised by reduced biosynthesis of melanin in the skin, hair and eyes. This disorder is analogous to the pink-eyed dilution phenotype seen in mice with defective Oca2 (Toyofuku et al. 2002). A single SNP in the OCA2 gene is the major determinant of brown and/or blue eye colour (Sturm 2009).

The membrane-associated transporter protein SLC45A2 (melanoma antigen AIM1, MATP) shows sequence and structural similarity to sucrose transport proteins yet its actual physiological substrate and role is still unclear. Mutations in SLC45A2 cause misrouting of tyrosinase similar to the cellular phenotype of OCA2 and cause oculocutaneous albinism type 4 (OCA4) (Cullinane et al. 2011).

Followed by: Leucodopachrome, L-Dopaquinone transform to Dopachrome, L-Dopa, Dopaquinone transforms to Leucodopachrome (Cyclodopa)

Literature references

Hearing, VJ., Ekel, TM., Montague, PM., Nicholson, JM. (1980). Mammalin tyrosinase. Stoichiometry and measurement of reaction products. *Biochim. Biophys. Acta, 611*, 251-68. ↗

Potterf, SB., Furumura, M., Sviderskaya, EV., Santis, C., Bennett, DC., Hearing, VJ. (1998). Normal tyrosine transport and abnormal tyrosinase routing in pink-eyed dilution melanocytes. *Exp. Cell Res., 244*, 319-26. ↗

Toyofuku, K., Valencia, JC., Kushimoto, T., Costin, GE., Virador, VM., Vieira, WD. et al. (2002). The etiology of oculocutaneous albinism (OCA) type II: the pink protein modulates the processing and transport of tyrosinase. *Pigment Cell Res., 15*, 217-24. ↗

Sturm, RA. (2009). Molecular genetics of human pigmentation diversity. *Hum. Mol. Genet., 18*, R9-17. ↗

Cullinane, AR., Vilboux, T., O'Brien, K., Curry, JA., Maynard, DM., Carlson-Donohoe, H. et al. (2011). Homozygosity mapping and whole-exome sequencing to detect SLC45A2 and G6PC3 mutations in a single patient with oculocutaneous albinism and neutropenia. *J. Invest. Dermatol., 131*, 2017-25. ↗

Editions

2015-01-13	Authored	Jupe, S.
2015-02-10	Edited	Jupe, S.
2015-02-13	Reviewed	Ito, S., d'Ischia, M.
2016-07-08	Revised	Jassal, B.

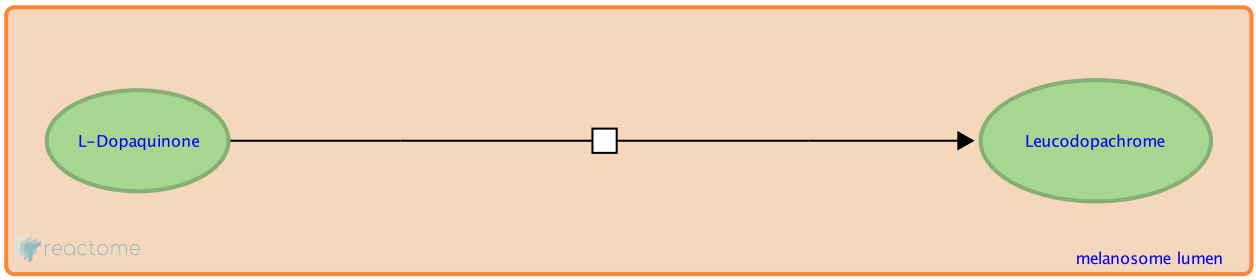
Dopaquinone transforms to Leucodopachrome (Cyclodopa) ↗

Location: Melanin biosynthesis

Stable identifier: R-HSA-5662669

Type: transition

Compartments: melanosome lumen



Dopaquinone is highly reactive and in the absence of sulfhydryl compounds it undergoes the intramolecular addition of the amino group to produce an intermediate, leucodopachrome (also termed cyclodopa). A redox exchange between cyclodopa and dopaquinone then gives rise to dopachrome, an orange-red intermediate (Raper 1927, Mason et al. 1948) and dopa. This latter reaction is considered the source of dopa formed during melanogenesis (Ito & Wakamatsu 2008).

Preceded by: Tyrosinase oxidises tyrosine to dopaquinone

Followed by: Dopachrome transforms to DHI, Dopa is oxidized to dopaquinone by TYR, Leucodopachrome, L-Dopaquinone transform to Dopachrome, L-Dopa

Literature references

Mason, HS. (1948). The chemistry of melanin. III. Mechanism of the oxidation of dihydroxyphenylalanine by tyrosinase. *J. Biol. Chem., 172*, 83-99. ↗

Editions

2015-01-13	Authored	Jupe, S.
2015-02-10	Edited	Jupe, S.
2015-02-13	Reviewed	Ito, S., d'Ischia, M.

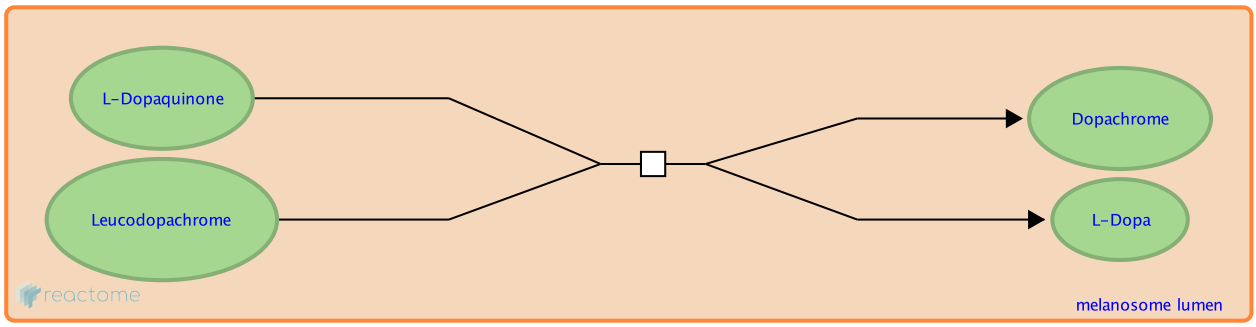
Leucodopachrome, L-Dopaquinone transform to Dopachrome, L-Dopa ↗

Location: Melanin biosynthesis

Stable identifier: R-HSA-5672019

Type: transition

Compartments: melanosome lumen



A redox exchange between leucodopachrome (cyclodopa) and dopaquinone gives rise to dopachrome, an orange-red intermediate (Raper 1927, Mason et al. 1948) and dopa. This reaction is considered the source of dopa formed during melanogenesis (Ito & Wakamatsu 2008).

Preceded by: Tyrosinase oxidises tyrosine to dopaquinone, Dopaquinone transforms to Leucodopachrome (Cyclodopa)

Followed by: Dopachrome is transformed to DHICA by DCT

Literature references

Mason, HS. (1948). The chemistry of melanin. III. Mechanism of the oxidation of dihydroxyphenylalanine by tyrosinase. *J. Biol. Chem., 172*, 83-99. ↗

Editions

2015-01-13	Authored	Jupe, S.
2015-02-10	Edited	Jupe, S.
2015-02-13	Reviewed	Ito, S., d'Ischia, M.

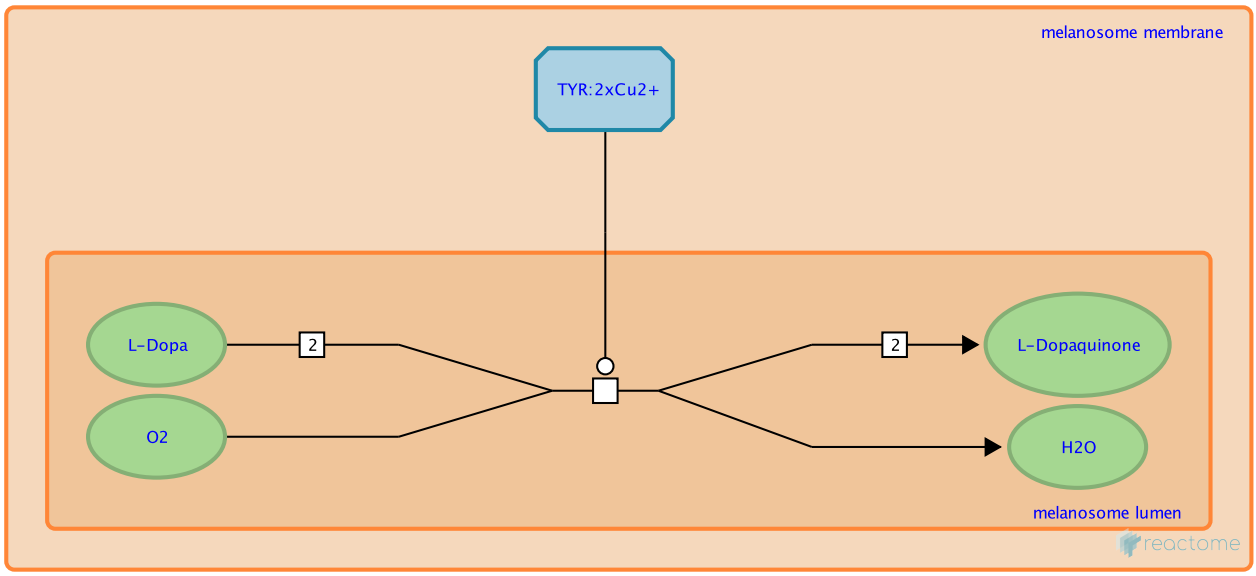
Dopa is oxidized to dopaquinone by TYR ↗

Location: Melanin biosynthesis

Stable identifier: R-HSA-5662692

Type: transition

Compartments: melanosome lumen



Dopa is a substrate of tyrosinase, which can oxidize it to dopaquinone (Young et al. 1974).

Preceded by: Dopaquinone transforms to Leucodopachrome (Cyclodopa)

Followed by: Dopaquinone, cysteine form CD isomers

Literature references

Young, TE., Griswold, JR., Hulbert, MH. (1974). Melanin. I. Kinetics of the oxidative cyclization of dopa to dopachrome. *J. Org. Chem., 39*, 1980-2. ↗

Editions

2015-01-13	Authored	Jupe, S.
2015-02-10	Edited	Jupe, S.
2015-02-13	Reviewed	Ito, S., d'Ischia, M.

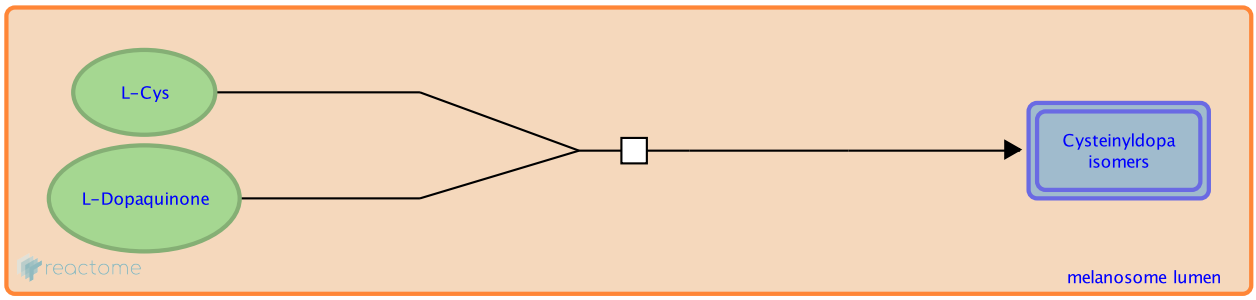
Dopaquinone, cysteine form CD isomers ↗

Location: Melanin biosynthesis

Stable identifier: R-HSA-5662908

Type: transition

Compartments: melanosome lumen



In the presence of sulfhydryl compounds such as cysteine, dopaquinone reacts to produce several cysteinyldopa (CD) isomers, 5-S-cysteinyldopa (5SCD) and 2-S-cysteinyldopa (2SCD) in 74% and 14% yields, respectively (Ito & Prota 1977, Thompson et al. 1985). 2,5-S,S'-dicysteinyldopa (DiCD) is produced in a 5% yield. Further oxidation of the thiol adducts leads to the formation of pheomelanin via benzothiazine intermediates.

Preceded by: Dopa is oxidized to dopaquinone by TYR

Followed by: CD isomers transform to BT, BTCA, BZ, ODHBT

Editions

2015-01-13	Authored	Jupe, S.
2015-02-10	Edited	Jupe, S.
2015-02-13	Reviewed	Ito, S., d'Ischia, M.

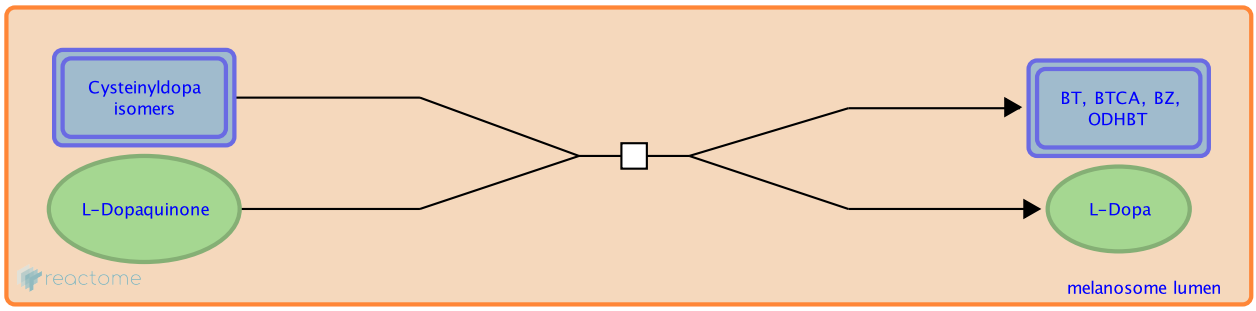
CD isomers transform to BT, BTCA, BZ, ODHBT ↗

Location: Melanin biosynthesis

Stable identifier: R-HSA-5662904

Type: transition

Compartments: melanosome lumen



Following the formation of cysteinyldopa (CD) isomers, pheomelanogenesis continues with the redox exchange of CD isomers with dopaquinone (DQ), generating cysteinyldopaquinone (CDQ). Once formed, CDQ rapidly cyclizes via attack of the cysteinyl side-chain amino group on the carbonyl group to produce a cyclic ortho-quinonimine intermediate (QI) (Napolitano et al. 1994, Land & Riley 2000). Redox exchange between CD and QI leads to the production of a reduced form of QI, 3,4-dihydro-1,4-benzothiazine-3-carboxylic acid (DHBTCA) and CDQ (Napolitano et al. 2000, Wakamatsu et al. 2009).

QI rapidly undergoes rearrangement, with or without decarboxylation, leading to 2H-1,4-benzothiazine (BT) and its 3-carboxy derivative, 2H-1,4-benzothiazine-3-carboxylic acid (BTCA) (Napolitano et al. 1994, 2008). The ratio of BT to BTCA depends on many factors including the pH of the medium and the presence or absence of metal ions (Di Donato et al. 2002, Napolitano et al. 2000). BT and BTCA are unstable, decaying in seconds. Modifications of the benzothiazine moiety of BT and BTCA lead to the formation of 3-oxo-3,4-dihydro-1,4-benzothiazine (ODHBT) and benzothiazole (BZ) (Napolitano et al. 1999, 2008).

The reactions beyond BT and BTCA which ultimately lead to the production of pheomelanin appear to be very complex (Di Donato & Napolitano 2003). Zn2+ promotes retention of the carboxyl group in BTCA while Fe3+ accelerates the ring contraction of BT to BZ (Di Donato et al. 2002). Production of ODHBT is increased by the presence of hydrogen peroxide (Di Donato et al. 2002).

Preceded by: Dopaquinone, cysteine form CD isomers

Followed by: pheomelanin formation

Literature references

Land, EJ., Riley, PA. (2000). Spontaneous redox reactions of dopaquinone and the balance between the eumelanic and phaeomelanic pathways. *Pigment Cell Res., 13*, 273-7. ↗

Editions

2015-01-13	Authored	Jupe, S.
2015-02-10	Edited	Jupe, S.
2015-02-13	Reviewed	Ito, S., d'Ischia, M.

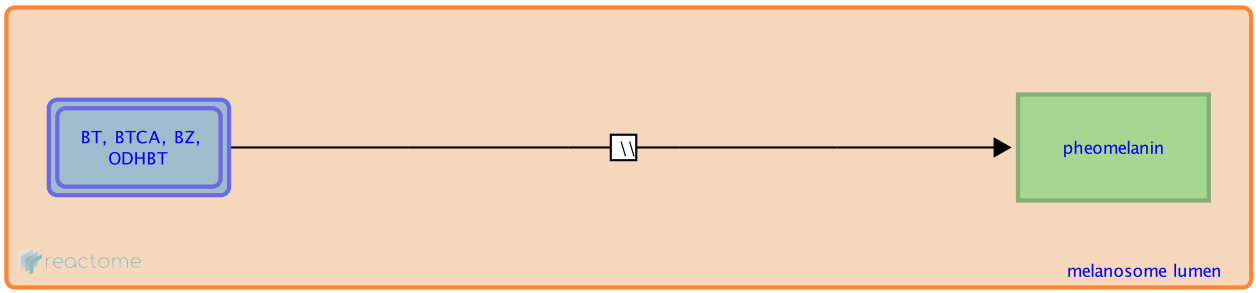
pheomelanin formation ↗

Location: Melanin biosynthesis

Stable identifier: R-HSA-5662891

Type: omitted

Compartments: melanosome lumen



The last stage of pheomelanogenesis is the oxidative polymerization of BT, BTCA, and the products of secondary modifications of the benzothiazine moieties of these to form pheomelanin. Several dimeric and trimeric intermediates have been identified (Napolitano et al. 2001) but it is unclear whether these are major components of natural pheomelanin pigments. Most studies have used powerful chemical oxidants (Di Donato et al. 2002, Napolitano et al. 2008). which may lead to a pheomelanogenesis process that differs from the in vivo process (Wakamatsu et al. 2008).

Preceded by: CD isomers transform to BT, BTCA, BZ, ODHBT

Literature references

Wakamatsu, K., Ohtara, K., Ito, S. (2009). Chemical analysis of late stages of pheomelanogenesis: conversion of dihydrobenzothiazine to a benzothiazole structure. *Pigment Cell Melanoma Res, 22*, 474-86. ↗

Editions

2015-01-13	Authored	Jupe, S.
2015-02-10	Edited	Jupe, S.
2015-02-13	Reviewed	Ito, S., d'Ischia, M.

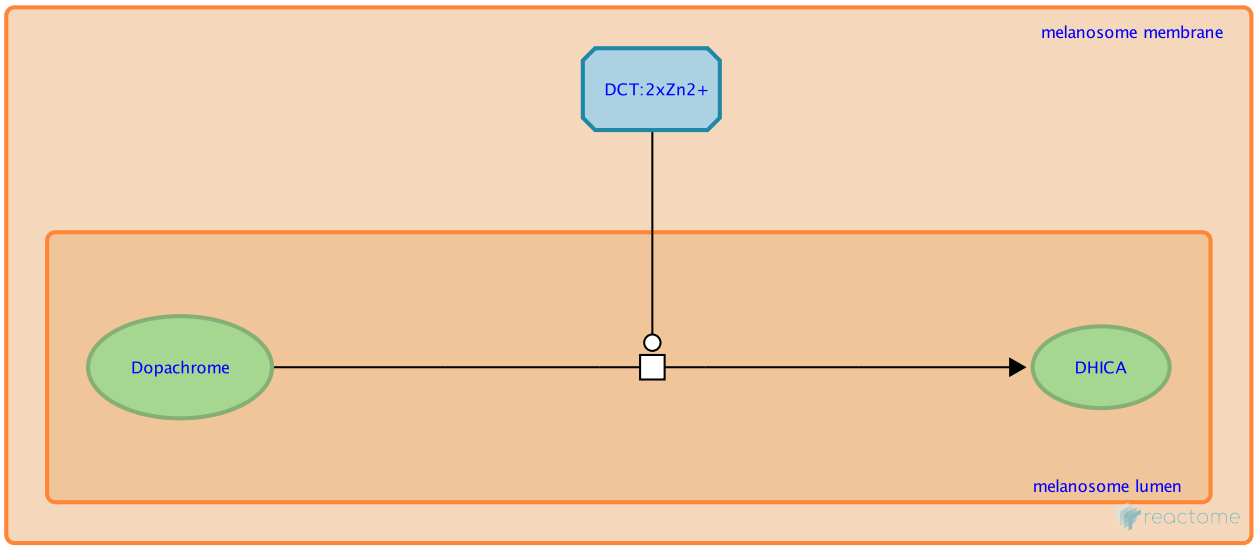
Dopachrome is transformed to DHICA by DCT ↗

Location: Melanin biosynthesis

Stable identifier: R-HSA-5662660

Type: transition

Compartments: melanosome lumen, melanosome membrane



Dopachrome is converted to DHICA by DCT (Dopachrome tautomerase, Tyrosinase-related protein 2) (Tsukamoto et al. 1992, Kroumpouzos et al. 1994, Bouchard et al. 1994).

Preceded by: Leucodopachrome, L-Dopaquinone transform to Dopachrome, L-Dopa

Followed by: DHI and DHICA polymerise forming eumelanin, TYRP1 oxidises DHICA to IQCA

Literature references

Kroumpouzos, G., Urabe, K., Kobayashi, T., Sakai, C., Hearing, VJ. (1994). Functional analysis of the slaty gene product (TRP2) as dopachrome tautomerase and the effect of a point mutation on its catalytic function. *Biochem. Biophys. Res. Commun., 202*, 1060-8. ↗

Editions

2015-01-13	Authored	Jupe, S.
2015-02-10	Edited	Jupe, S.
2015-02-13	Reviewed	Ito, S., d'Ischia, M.

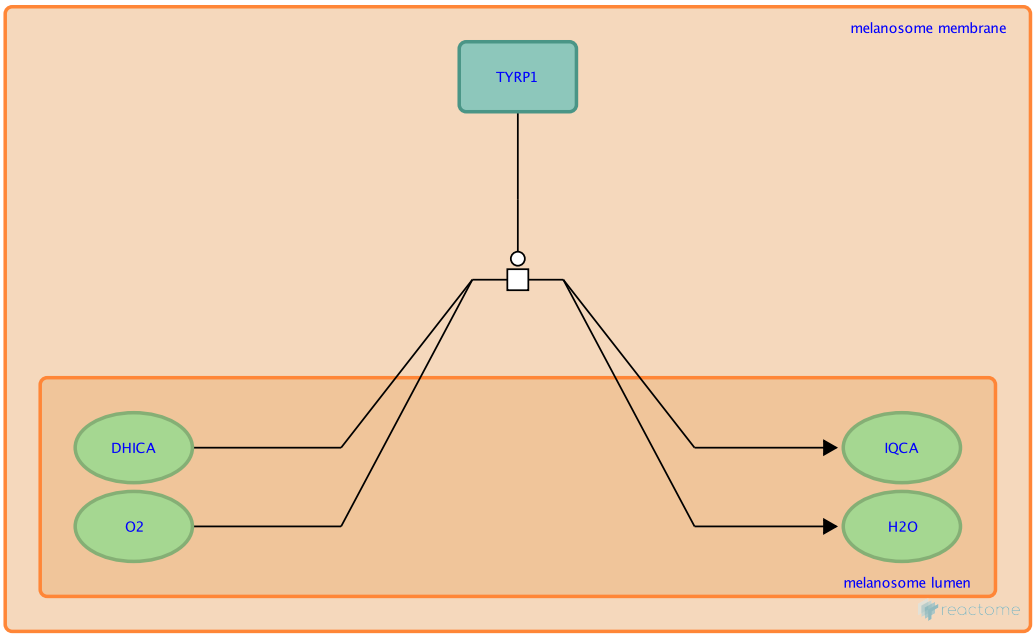
TYRP1 oxidises DHICA to IQCA ↗

Location: Melanin biosynthesis

Stable identifier: R-HSA-8878581

Type: transition

Compartments: melanosome membrane, melanosome lumen



5,6-dihydroxyindole-2-carboxylic acid oxidase (TYRP1, aka gp75, CAS2, TRP-1) is an abundant protein in the melanosome membrane which, amongst other functions, can oxidise 5,6-dihydroxyindole-2-carboxylic acid (DHICA) into the corresponding 5,6-indolequinone-2-carboxylic acid (IQCA), thus promoting the incorporation of DHICA units into eumelanin (Olivares et al. 2001). Oculocutaneous albinism (OCA) is an autosomal recessive disorder caused by either complete lack of or a reduction of melanin biosynthesis in melanocytes. Mutations in TYRP1 cause OCA3, aka Rufous oculocutaneous albinism. Tyrosinase activity is normal and patients have only a moderate reduction of melanin. Darker-skinned sufferers have bright copper-red colouration of the skin and hair (Kamaraj & Purohit 2014, Rooryck et al. 2006).

Preceded by: Dopachrome is transformed to DHICA by DCT

Literature references

Olivares, C., Jiménez-Cervantes, C., Lozano, JA., Solano, F., García-Borrón, JC. (2001). The 5,6-dihydroxyindole-2-carboxylic acid (DHICA) oxidase activity of human tyrosinase. *Biochem. J., 354*, 131-9. ↗

Kamaraj, B., Purohit, R. (2014). Mutational analysis of oculocutaneous albinism: a compact review. *Biomed Res Int, 2014*, 905472. ↗

Rooryck, C., Roudaut, C., Robine, E., Müsebeck, J., Arveiler, B. (2006). Oculocutaneous albinism with TYRP1 gene mutations in a Caucasian patient. *Pigment Cell Res., 19*, 239-42. ↗

Editions

2016-07-11	Authored, Edited	Jassal, B.
2016-08-12	Reviewed	D'Eustachio, P.

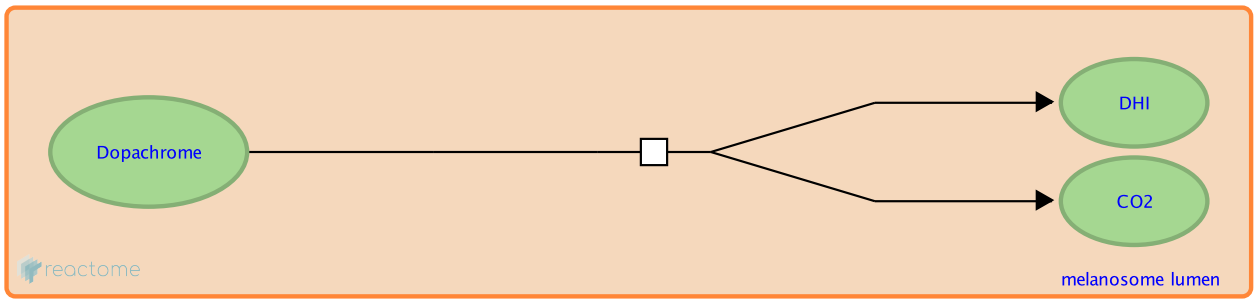
Dopachrome transforms to DHI ↗

Location: Melanin biosynthesis

Stable identifier: R-HSA-5662706

Type: transition

Compartments: melanosome lumen



Dopachrome spontaneously tautomerizes into 5,6-dihydroxyindole (DHI) via decarboxylation at physiological pH (Mason et al. 1948, Wakamatsu & Ito 1988, Kishida et al. 2015). This is usually a minor process of melanin synthesis in vivo. However, in human hair follicular melanocytes, it predominates (Commo et al. 2012).

Preceded by: Dopaquinone transforms to Leucodopachrome (Cyclodopa)

Followed by: DHI and DHICA polymerise forming eumelanin

Literature references

Mason, HS. (1948). The chemistry of melanin. III. Mechanism of the oxidation of dihydroxyphenylalanine by tyrosinase. *J. Biol. Chem., 172*, 83-99. ↗

Editions

2015-01-13	Authored	Jupe, S.
2015-02-10	Edited	Jupe, S.
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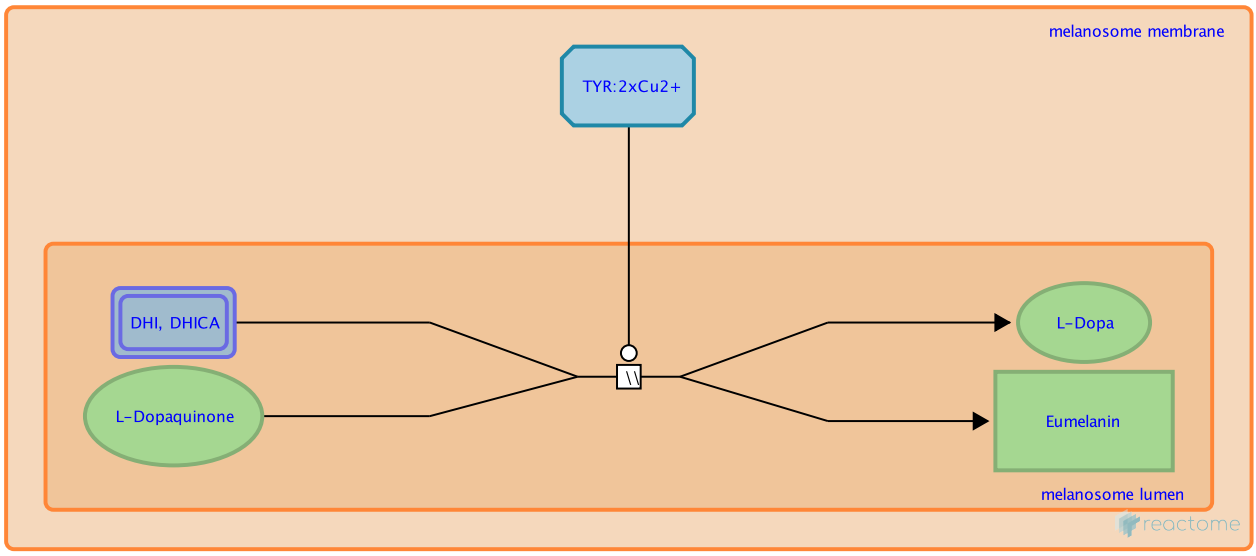
DHI and DHICA polymerise forming eumelanin ↗

Location: Melanin biosynthesis

Stable identifier: R-HSA-5663050

Type: omitted

Compartments: melanosome lumen, melanosome membrane



Eumelanin is a stacked, aggregated oligomer, or heterogeneous polymer consisting of units representing different oxidative states of 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA), plus pyrrole units derived from their peroxidative cleavage (Meredith & Sarna 2006, Ito & Wakamatsu 2008). Eumelanin was thought to consist mostly of DHI but this was reconsidered when chemical degradation revealed that natural eumelanins include DHI and DHICA units in a nearly equal ratio (Ito 1986, d'Ischia et al. 2013). DHICA is produced by tautomerization of dopachrome.The oxidative polymerization of DHI can be catalyzed by Tyrosinase (TYR) (Tripathi et al. 1992) but may also be effectively catalysed by redox exchange with dopaquinone (Edge et al. 2006). Redox is likely to be less efficient for DHICA. In mice, the tyrosinase-related protein Tyrp1 can oxidize DHICA (Kobayashi et al. 1994) but human TYRP1 is unable to catalyze the same reaction (Boissy et al. 1998). Instead, human TYR oxidizes DHICA, DHI, tyrosine and dopa.

Preceded by: Dopachrome is transformed to DHICA by DCT, Dopachrome transforms to DHI

Literature references

Meredith, P., Sarna, T. (2006). The physical and chemical properties of eumelanin. *Pigment Cell Res., 19*, 572-94. ↗

Editions

2015-01-13	Authored	Jupe, S.
2015-02-10	Edited	Jupe, S.
2015-02-13	Reviewed	Ito, S., d'Ischia, M.

Table of Contents