A Review on a Bio-Synthetic Pathway: Melanogenesis

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ABSTRACT

Melanogenesis is a complex process that involves many genes which leads to production and distribution of the melanin pigment. Melanin is a dark biological pigment derived by the oxidation and subsequent polymerization of phenolic compounds. There are two types of melanin viz., eumelanin (black-brown color) and pheomelanin (yellow-red color). Melanin is found in different parts of the body of the animal like skin, brain, eye, ear and perform different functions apart from pigmentation. The main biosynthetic pathway of melanogenesis in all animals is Raper-Mason pathway. Melanogenesis pathway is regulated by different pathways which involve many genes like MC1R, AC, β-catenin, RAS, BRAF, MAPK, MITF etc. Melanin has very unique properties like redox capacity, metal chelating properties or free radical scavenging properties etc. Because of these properties Melanin and melanin like materials (PDA-polydopamine) have different applications in the field of dermatology, cosmetics, biomedicine as well as anti-pollution product technologies and many more. This review presents a general overview of melanin and melanogenesis in different types of organisms and applications of melanin in different biological fields.

Keywords
Melanogenesis, Eumelanin, Pheomelanin, Polydopamine, Biological application

Introduction

Melanogenesis by definition is the production of the melanin pigments; which is produced by cells called melanocytes (D’Mello et al., 2016). The epidermal units of the skin are responsible for melanin production and distribution by the melanogenesis process. There are many proteins, hormones and enzymes are involved in melanogenesis process which may be regulating the melanin production directly or indirectly (Videira et al., 2013).

Over the past decade, melanin and melanogenesis have been increasingly valued not only for the pigment related study but also studied as a source of novel research opportunities in the fields of dermo cosmetics, biomedicine, nanotechnology, and other...
biotechnological fields. The purpose of this study is to give a brief overview of the melanin, the pathway and genes involved in melanogenesis, the biological functions, synthesis procedure, application and also the disorders associated with this to attract significant research interest from researcher in the fields of biological, chemistry and medicine.

**Melanin- definition**

The name “melanin” comes from the ancient Greek word “melanos”, meaning “dark”. The term was first used by the Swedish chemist Berzelius in 1840 to call a dark pigment extracted from eye membranes.

Melanin is considered as a heterogeneous polymer produced from the oxidation of phenol and subsequent polymerization of intermediate phenols and their resulting quinones (Nicholas et al., 1964). Melanin is of two types-1. Eumelanin (Black or Brown), 2. Pheomelanin (Yellowish to Reddish-brown) formed by the conjugation of cysteine or glutathione (Slominski et al., 2004).

Eumelanin is dominant in the individuals with dark skin and hair and is more effective in photo protection. Pheomelanin is predominantly found in individuals with red hair and skin, in whom skin tumour is more common as it is less efficient in photo protection.

**Biological functions of melanin in different animals**

Melanin, the well-known biopolymers are distributed widely in animals, microorganisms, plants, and play significant physiological roles (Solano, 2014). Some of the important functions are described in Table 1.

**Genes involved in melanogenesis**

Melanogenesis is a complex process which is regulated by many genes (Videira et al., 2013). In order to understand the pathogenicity of pigmentation disorders and subsequent development of potential therapeutic options, there is an urge for correct identification and comprehension of the genes regulating the mechanism of melanogenesis. Table 2 represents the list of different genes involved in melanogenesis and those which are responsible for melanin synthesis and regulation.

**Biochemical pathways for melanogenesis**

According to variations in the structure and occurrence of melanin, its biogenesis is not a single and universal process. The study on various organisms led several biosynthetic pathways in melanin synthesis (Solano, 2014). The general features in all the pathways involve an initial phase with the enzymatic-catalyzed oxidation of phenolic precursors to quinones followed by a final phase consisting of the mostly unregulated polymerization of quinones. The different bio synthetic pathways of different organisms are mentioned in Table 3. The most universal and well-known pathway of animal is called the Raper-Mason pathway which is described below.

**Raper-mason pathway of melanogenesis**

The initiation process of melanogenesis begins by virtue of the key enzyme, Tyrosinase (TYR) which oxidizes L-tyrosine to DopaQuinone (DQ). The resulting DopaQuinone (DQ) will serve as a substrate for the synthesis of eumelanin and pheomelanin (Fig. 1).
Eumelanin synthesis

The formation of DQ is a rate-limiting step in the melanin synthesis. After DQ formation, it undergoes intramolecular cyclization to produce indoline, leukodopachrome (cyclo dopa).

The redox exchange between leukodopachrome and DQ give rise to dopachrome and L-3,4-dihydroxyphenylalanine (L-DOPA). L-DOPA is also a substrate for TYR and oxidized to DQ again by the enzyme. Dopachrome gradually decomposes to give dihydroxyindole (DHI) and dihydroxyindole-2-carboxylic acid (DHICA). The later process is catalyzed by TYRP-2 (Tyrosinase Related Protein-2) or Dopachrome tautomerase (DCT).

Ultimately, these dihydroxyindoles (DHI and DHICA) are oxidized to eumelanin. TYRP-1 (Tyrosinase Related Protein-1) is catalyze the oxidation of DHICA to Indole-5,6-Quinone Carboxylic Acid (IQCA), which is a structural unit of eumelanin (Fig. 2).

Pheomelanin synthesis

DQ is converted to 5-S-cysteinyldopa or glutathionyldopa in the presence of cysteine or glutathione. Subsequent oxidation gives benzothiazine intermediates and finally produces pheomelanin.

Regulation of melanogenesis

Regulation of melanogenesis at the subcellular level where the gene expression encoded by the melanogenesis-related enzymes including TYRP-1, TYRP-2 and TYR is regulated by intracellular pathways.

These signal pathways are initiated by a variety of hormones which gives complex signals that responds to UV exposure or other environmental stimulations. There are three most commonly known signal pathways involved in the regulation of melanogenesis (Pillaiyaret al., 2015)-

cAMP (Cyclic Mono Phosphate)-dependent signalling pathway
Wnt signalling pathway
ERK (Extracellular Signal-Regulated Kinase) signalling pathway

All three signal pathways involve Microphthalmia-associated transcription factor (MITF)(Vance and Goding, 2004).

Microphthalmia associated transcription factor (MITF)

MITF is the master regulator of melanogenesis (Pogenberget al., 2012).

MITF is a basic helix-loop-helix leucine zipper transcription factor protein that encodes 520 amino acids, this protein is encoded by MITF gene consisting of 1563 nucleotides.

It has basic domain which is used for DNA binding (Figure- 3).

HLH and Zip domains that are used for homo- and/or heterodimer formation.

It binds to the M box of a promoter region (3’-CANNTG-5’) of the pigmented gene tyrosinase (TYR), TYRP-1 (Tyrosinase Related Protein-1) and TYRP-2 (Tyrosinase Related Protein-2) and regulates their expression.

MITF is also regulates the expression of Bcl2 (B-cell lymphoma 2) which is involved in the survival, proliferation, and differentiation of melanocytes cells
Genes involved and diseases associated with abnormal melanogenesis

There are many genes involved in the melanogenesis pathway. Mutation of these genes leads to different melanogenic disorders which are tabulated in Table 4.

Melanin synthesis: natural and synthetic

Extraction and purification of natural melanin

There are many different methods which are involved for melanin extraction form different natural sources. The methods are like chemical extraction and purification, matrix-assisted laser desorption, ionization mass-spectrometry or pyrolysis gas chromatography etc. The different sources of natural melanin synthesis and the extraction procedures are tabulated in table 5.

Synthetic melanins by oxidation of L-Dopa

There are also melanins formed by chemical oxidation from some diphenolic precursors of melanogenesis pathway, like L-3,4-dihydroxyphenylalanine (L-DOPA), which is commercially available. The produced melanin known as dopa-melanin and dopamine-melanin, which are easily formed by chemical oxidation of those precursors by generally using atmospheric oxygen or hydrogen peroxide in basic media.

Autoxidation of L-Dopa was obtained by dissolving L-Dopa up to saturation in salt free aqueous solution (for example- borate buffer) at different pH and stirred in air.

After polymerization of sample, it is finally prepared under different conditions of ionic strength (Bridelli, 1998). Enzymatic oxidation of L-Dopa is synthesized by the tyrosinase (Example- Mushroom Tyrosinase), which is the main enzyme involved in melanogenesis. The aqueous solution is buffered at neutral pH and stirred in air for some days to get polymerized synthetic melanin (Bridelli, 1998).

Samples obtained both by autoxidation and by enzymatic polymerization appeared as black-brown solutions which contain mixtures of granules of different average sizes, depending on the pH in the buffer solution. After polymerization and dilution, the sample is then analysed for the polymerization kinetics. The synthetic melanin is used as model melanin for biophysical studies and other applications of eumelanin.

Applications of melanin

Over the past decades, applications of melanin and melanogenesis have been increasingly adapted apart from the pigment cell community. They are used as a source of novel research opportunities in the fields of biomedicine, dermo-cosmetics, nanotechnology, materials science etc. The different applications of melanin were previously reviewed by many researchers (d’Ischia et al., 2015; Solano, 2017; Huang et al., 2018; Qi et al., 2019). In this study some of the applications are described below.

Dermocosmetic applications

Dermo-cosmetic applications of melanin and melanogenesis include mainly the modulation of the melanogenesis pathway to control skin color like hyperpigmentation. Hyperpigmentation occurs in response to UV-induced DNA damage, inflammation, or other skin injuries etc.

Modulation of melanogenesis to alter the colour and its pattern is passion which has lot of demand and application in human medicine and cosmetics. Literature review suggested that a number of studies has been carried related to the identification of melanogenesis
modulators, both natural and synthetic and have been used in cosmetics products as hypopigmentation agents (Chang, 2012; Pillaiyar et al., 2015).

**Melanin precursor as hair dye**

Colour fading, hair damage or complication in handling, these are some common problems occurred by using of conventional or traditional oxidative hair dyes. As an alternative the natural melanin precursor, like-DHI, DHICA can be used as hair dye. These precursors can be converted into the natural melanin by air oxidation and can be easily penetrate into the hair (d’Ischia et al., 2015).

Although using of this precursor is commercially appealing, but it is methodologically challenging because of the difficulty to obtain a natural hue in the final dye, the relatively low affinity for hair and also penetration is sometimes low.

A valuable biotechnological approach to cover gray hair with melanin precursors by enzymatic oxidation has been developed using a fungus, *Aspergillus oryzae* (Nakamura et al., 2012). Recent research showed that purified DOPA (one of the precursor product of melanogenesis) is used for the production of DHI and tyrosinase enzyme of *Aspergillus oryzae* is used as oxidative enzyme to produce melanin from DHI. The formulation leads to lower levels of hair damage than with traditional oxidative hair dyes and the skin staining level is lower than with direct dye systems (Koike and Ebato, 2013).

**Melanin in antioxidant therapy**

PDAM nanoparticles have been frequently proposed as powerful antioxidants, to protect against damage by free radicals, ROS (Reactive Oxygen Species) and RONS (reactive oxygen and nitrogen species). The nanoparticles display good stability in water and stronger free radical scavenging activity, to slow down the oxidation rate. PDAM has been proposed for treatment of severe diseases related to oxidative stress, such as neurologic disorders and inflammatory diseases (Liu et al., 2017).

**Melanin in photothermal therapy**

Photo-thermal therapy (PTT) is an effective therapeutic treatment that has nowadays used to treat the solid cancer as it has deep tissue penetration and it shows minimal effects on the surrounding healthy tissues. This method
relies on activation of photosensitizing agents which absorb energy and converts into heat by an electromagnetic radiation like microwave, radio frequencies, visible light etc. Due to a high absorption capacity in the infrared region, high conversion ability of that energy to heat and also significant stability to irradiation, PDAM is used widely in PTT to cure cancer (Liu et al., 2013). Another importance of using PDAM nanoparticles is, it is able to kill tumour cells in animal models with short irradiation laser times (Liu et al., 2013).

Table 1 The general roles/functions of melanin in different organisms

| Organism/org an | Role/function |
|-----------------|---------------|
| Cutaneous Melanin | Sunscreen Photo-protector Colour determination |
| Ear Melanin | Appropriate hearing (Gottesberge, 1988) Biological reservoir of divalent ion Calcium homeostasis |
| Neuro Melanin | Toxic element protection Chelate metal ions (Fe) produced in brain (Sealy, 1984) |
| Eye Melanin | Greater visual activity Protect retina from Sunlight and Photo-oxidation (Hosseini et al., 2010) |
| Bird feather melanin | Photo protection Abrasion protection Increase long life of feather (Bonser, 1995) Help in mate choice |
| Amphibian & Fish melanin | Thermoregulation Camouflage, mate choice, species recognition Protect from predators |
| Insects Melanin | Strengthen exocuticle Defend against microbial infection (Sugumaran, 1998) Shell hardening as the egg matures Ex-helminthes |
| Microorganism melanin | Protector of very stressful conditions. Ex-Chernobyl Helps in endospore formation. Ex-Bacillus Protects from chemical compounds Ex- Bacillus thuringiensis (Aghajanyan et al., 2005) |
### Table 2 List of genes responsible for melanogenesis

| Gene   | Protein                                  | Function                                                                                                                                 |
|--------|------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| MITF   | Microphthalmia Associated Transcription Factor | Transcription factor which regulates function of pigmentary enzymes and survival of melanocytes                                           |
| PAX3   | Paired box gene 3                        | Proliferation, differentiation, survival of melanocyte                                                                                   |
| MC1R   | Melanocortin1 receptor                    | Receptor of α-MSH hormone, upregulates melanogenesis                                                                                     |
| AC     | Adenylate Cyclase                        | Increase cAMP level in melanocyte                                                                                                         |
| PKA    | Protein Kinase A                         | Phosphorylates transcription factors which activates MITF                                                                                 |
| β-Catenin | Beta catenin                             | Upregulates transcription of MITF                                                                                                          |
| C-kit  | Tyrosine kinase receptor                 | Melanocyte physiology, influencing melanogenesis, proliferation, migration, and survival of the pigment-producing cells.                |
| RAS    | Ras GTPase protein                       | Melanocyte cell growth, differentiation and survival by activating RAF protein                                                            |
| RAF    | RAF kinase protein                       | Melanocyte cell growth, differentiation and survival by activating MEK protein                                                              |
| MEK    | Mitogen-activated protein kinase kinase   | Activating ERK protein                                                                                                                    |
| ERK    | Extracellular signal-Regulated Kinase     | Negatively regulates activity of MITF protein by phosphorylate and ubiquitation                                                            |
| TYR    | Tyrosinase                               | Initiates melanin biosynthesis process                                                                                                     |
| TYRP1  | Tyrosinase Related Protein1              | DHICA-oxidase function in melanogenesis and regulates activity of TYR.                                                                       |
| TYRP2  | Tyrosinase Related Protein2              | Produce DHICA from Dopachrome which is a precursor product of melanin                                                                       |

### Table 3 Biochemical pathway of melanin synthesis in different organisms

| Organism | Pathway                                      | Precursor               | Main enzyme       | End product          |
|----------|----------------------------------------------|-------------------------|-------------------|----------------------|
| Animal   | Raper-Mason pathway of melanogenesis         | L-tyrosine              | Tyrosinase        | Eumelanin Pheomelanin|
| Plant    | Catechol melanin synthesis pathway           | Catechols, Caffeic acid | Catechol Oxidase   | Catecol-Melanin      |
| Fungal   | Pentaketide pathway                          | 1,8DiHydroxyNaphathalene(1,8-DHN) | Laccase           | DHN-melanins         |
**Table 4** Genes and Diseases associated with hypopigmentation (Spritz and Hearing, 2013)

| Gene | Disease                                      | Inheritance | Protein                                                       |
|------|----------------------------------------------|-------------|---------------------------------------------------------------|
| KIT  | Piebaldism                                   | Dominant    | Receptor tyrosine kinase                                     |
| MITF | Waardenburg syndrome(type II A)              | Dominant    | Microphthalmia (mi) associated Transcription Factor          |
| HPS1 | Hermansky–Pudlak syndrome I                  | Recessive   | BLOC-3 component (Biogenic Lysosome related organelles complex-3) |
| FOXD3| Generalized vitiligo                         | Dominant    | Neural crest melanoblast differentiation regulator            |
| TYR  | Oculocutaneous albinism type I               | Recessive   | Tyrosinase                                                   |
| OCA2 | Oculocutaneous albinism type II              | Recessive   | OCA2 melanosomal protein                                     |
| TYRP1| Oculocutaneous albinism type III             | Recessive   | DHICA oxidase/Tyrosinase Related Protein 1                    |
| SLC45A2|Oculocutaneous albinism type IV               | Recessive   | MATP(Membrane-associated transporter protein)                 |

**Table 5** Different types of extraction and purification procedures applied to various melanin types (Pralea et al., 2019)

| Melanin source | General method of Extraction and Purification                                                                                                                                                                                                 |
|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Fungal melanin**<br>Boletus griseus<br>(Liu et al., 2018)<br>Auricularia auricular<br>(Sun et al., 2016) | Incubation with basic medium (Ex- NaOH)<br>Centrifugation followed by pH adjustment<br>Again centrifugation and precipitate collection and washing in distilled water<br>Vacuum freeze-drying of the precipitate hydrolyzation (Ex-HCL)<br>Filtration and washing<br>Repeated solubilisation in basic medium of the precipitate followed by pH adjustment<br>Successive washing and vacuum freeze-drying of the precipitate |
| **Sepia ink**<br>(Wang and Rhim, 2019) | Dilution of sepia ink paste with distilled water using homogenizer<br>Centrifugation followed by washing of the suspension in acid medium<br>Drying at proper temperature to obtain dried melanin particles |
| **Human hair**<br>(Liu et al., 2003) | Repeated hair washing using proper chemical (Example-acetone, dichloromethane, ether and water)<br>Suspension of hair in proper buffer solution (Ex- phosphate) |
buffer) repeated overnight incubation by using protein degradation enzyme like proteinase K and or papain centrifugation followed by washing and re-suspension in buffer solution Triton X-100 treatment was done for protein extraction and then ultracentrifugation and washing with water At last overnight treatment with protein degradation enzymes like proteinase K Successive washing with water and drying to produce Melanin

| **Bacterial melanin**<br>*(Singh et al., 2018)* | Centrifugation of bacterial culture followed by acidification (Example- By using HCL) of the supernatant, produced from centrifugation Storage in the dark for some days, usually 7 days Then boiling is done followed by cooling and centrifugation Pellet wash with acid medium and distilled water Then storage at room temperature usually for 1 day After storage residue wash with ethanol followed by air dry |

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**Figure.1** Raper-mason pathway of melanogenesis
**Figure 2** Overall pathway of melanogenesis (melanogenesis pathway map of Kyoto Encyclopedia of Genes and Genomes)

**Figure 3** MITF protein dimer binds with DNA (Pogenberg et al., 2012)
Melanin nanoparticles as biomedicine

PDAM is an easy coating of nanoparticles, have a good ability to be conjugated with other materials, biocompatible in nature and can deliver properly nanoparticle-charged active agents to reach its specific targets. These nanoparticles are tailored to be carriers of specific anticancer drugs that should be first preloaded, and later released in the target tissues in response to appropriate stimuli. Previously PDAM nanoparticles have been loaded with anticancer drugs, such as doxorubicin and 7-ethyl-10-hydroxy camptothecin (Wang et al., 2016), or sorafenib (Zhang., 2015) to treat with cancer. Melanin shielded nanoparticles prepared by enzymatic polymerization on silica have been reported to provide excellent protection from radiotoxicity to bone marrow during radio-immunotherapy as well as in some other therapy like external beam radiation therapy, permitting the administration to tumours of significantly higher doses (Schweitzer et al., 2010).

Melanin in tissue engineering

The intrinsic electroactivity, biocompatibility, outstanding adhesive property, as well as high antioxidant activities of melanin and PDA make them ideal biomaterials for skeletal muscle tissue engineering. Designed biomaterial scaffolds employed by skeletal muscle tissue engineering (SMTE) promote myogenic differentiation of myoblasts to functional myotubes.

Manchineella et al., 2016 developed silk fibroin / melanin composite films and scaffolds for the promotion of Myogenesis. The incorporated melanin could modulate the thermal stability and electrical conductivity of these scaffolds, and impart the antioxidant properties to the scaffolds.

Due to their good adhesive properties, melanin coatings are useful for implantable biomaterials which can prevent material displacement from the site of implant. Melanin coated scaffold has the ability of both cancer therapy and bone regeneration (Ma et al., 2016).

Synthetic melanin as water purifier

A simple oxidation polymerization of 3,4-dihydroxy-phenylalanin (DOPA) along with KMnO₄, led to lucrative synthesis of spherical-shaped melanin nanoparticles.
having good water-dispersibility. Kim et al., (2012) investigated their binding ability with many heavy metal ions in aqueous solution and found the binding capacity to be maximum with copper, lead and cadmium. Thus, melanin nanoparticles can turn out to be excellent remediator of contaminated water due to its highly efficient and expeditious binding capacity to metal ions.

In conclusion, this study showed that melanin is a powerful bio-molecule that goes far beyond being just a cutaneous photoprotective pigment in skin. Melanogenesis, the process of melanin synthesis, is regulated by many genes. The importance of each of these genes and their mechanisms are evident in clinical genetic defects and the identification of these defects has contributed to a better understanding of the melanocyte biology and melanogenesis regulation. Recent advances on melanin applications suggest that both natural and synthetic like-molecules, is indeed excellent materials for bioelectronics and biomedical purposes, due to their unique properties like light absorbance, radical scavengers, ion chelating agent, polymers with strong binding capacity etc.

Despite all of these recent advancement and application, however, several challenges must be introduced before melanin-based technology becomes a developed field. There is a need to expand the efforts toward a deeper understanding of the conductivity properties of melanin to optimize their response for applications in organic electronics, bioelectronics and other more specific applications. These goals can be easily achieved through cooperation between researchers involved in academic, industrial, and clinical settings, which should encourage an increasing number of companies to invest on melanin research for innovative and sustainable solutions for human health and technology.

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