자연계에 존재하는 다기능성 소재 : 멜라닌

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Melanin: A Naturally Existing Multifunctional Material

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초 록
사람의 머리카락, 눈, 피부 등에서 발견되는 멜라닌은 자연의 생물체에 존재하는 어두운 색소를 가르치는 통칭이다. 멜라닌은 자유 라디칼을 흡수해서 제거하는 특성을 가지고 있어, 해로운 UV 광선이 생체로 침투할 때, 세포 및 조직을 보호하는 역할을 한다. 또한, 전기적 전도성 및 이온 전도성을 가지고 있으며, 항산화성, 껍질의 성장, 금속이온 감소 등을 다기능성으로 인해, 다양한 분야에서의 응용이 주목받고 있다. 자연계에 존재하는 생체 멜라닌의 구조를 정확하게 정의할 수는 없지만, 멜라닌의 응용 분야는 센서, 의료기기 등으로 확대되고 있다. 본 미니총설에서는 멜라닌의 원천과 합성, 구조와 특성 그리고 다양한 분야로의 응용 가능성에 대해서 구체적으로 논의한다.

Abstract
Melanin is a common name used for a certain type of natural dark pigments existing in living organisms, particularly in human hair, eyes, and skin. The unique free radical scavenging effect of melanine could help protecting cells and tissues from harmful UV light. While their exact molecular structures in nature are not still well defined, their multifunctional properties including electrical and ionic conductivities, antioxidation, wet adhesion, and metal ion chelation, are highlighted for the potential applications in bioorganic electronics including biomedical sensors and devices. In this mini-review, we will discuss sources, synthesis methods, structures and multifunctional properties of melanin materials in addition to current research directions on a wide range of applications.

Keywords: melanin, eumelanin, polydopamine, natural pigments, biocompatible, bioorganic electronics

1. Introduction

Melanin indicates broad ranges of natural biopolymeric pigments, whose name is originated from melanos (dark in Greek) by Swedish chemist Berzelius (1840)[1]. In nature, melanin exist in five different structural forms and functional types; eumelanin, pheomelanin, allomelanin, pyomelanin, and neuromelanin[2,3]. In Figure 1, various precursors for synthesizing these melamins are shown. Melanin, particularly eumelanin, has been unveiled to hold unique multifunctional properties including broadband UV - visible light absorption [4,5], paramagnetism, electrical conductivities[6-11], biocompatibility, biodegradability[12], radical scavenging[13], and metal ion chelating[14]. While eumelanin particles, such as sepia inks from cuttlefish, are not well characterized due to their extreme insolubility, polydopamine is a major component of its eumelanin particles whose molecular functional groups include catechol, amine, and imine. Combined with eumelanin’s versatile functions, these chemically crosslinking anchors provide extreme usability from simple coating materials to complex chemical, biological, and medical sciences. The fabrication of melanin materials has been recently activated by demonstrating, for examples, composites, films, hydrogels, and membranes. Thus, the unprecedentedly wide ranges of melanin applications include sensors, batteries, supercapacitors, solar cells, drug delivery, bioimaging, diagnosis, tissue engineering, and medical implants. The purpose of this review is to present the recent research trends of melanin by elucidating molecular structures functional properties, and devices applications, and to encourage the researches of this material.
2. Structures of Natural and Synthetic Melanin

2.1. Natural melanin

In nature, there exist in five different kinds of melanin; eumelanin, pheomelanin, allomelanin, pyomelanin, and neuromelanin.

Eumelanin is a black-to-brown pigment such as in cuttlefish ink and human black hair. Eumelanin is polymerized by oxidation of L-tyrosine or L-dopa via 5,6-dihydroxyindole (DHI) or 5,6-dihydroxyindole-2-carboxylicacid (DHICA) intermediates (Figure 2). Large quantity of eumelanin can be extracted from cuttlefish ink (Figure 3). Unlike other melanin, eumelanin shows electrical conductivities and paramagnetism. Furthermore, eumelanin has unique properties such as radical scavenging, metal ion binding and photoelectronic properties. Because of this multifunctional property, eumelanin is the key objective materials for the recent studies to make functional devices.

Pheomelanin is a yellowish-to-reddish pigment in red hair, freckles, and feathers of birds. Pheomelanin is polymerized by oxidation of 5-S-Cys-dopamine and 5-S-Cys-dopa (L-tyrosine is polymerized with L-cysteine), the main difference from eumelanin is presence of sulfur in aromatic ring structures.

Allomelanin is a dark brown-to-totally black pigment in plant. Allomelanin is a polymer devoid of nitrogen. Because it is derived from catechol by catechol oxidase, allomelanin is also named as catechol-melanin. This melanin was reported as preventer of the undesirable browning of plants.

Pyomelanin is a dark pigment in fungal metabolite (Pseudomonas and Aspergillus fumigatus), derived from homogentisic acid (HGA). The molecular structure of this melanin is similar to eumelanin.

Neuromelanin is a dark pigment present in human brain, mostly situated in Substantia nigra and in lower of the Locus coeruleus. This melanin consists of pheomelanin, which formed in the core of the granule, and eumelanin, which formed on the surface[2,3].
2.2. Synthetic melanin

Synthetic melanin is generally polymerized by oxidation of L-dopa, L-dopamine, DHI, and DHICA as precursors with the catalytic reaction of tyrosinase, peroxidase, and hydrogen peroxide, or in a basic pH condition (pH > 7.5) with oxygen as the oxidant[2,3,5,8,11,14,18,19](Figure 5). Particularly, oxidation of pure dopamine occurs to be polydopamine, eu-melanin-like polymer, which has unique wet adhesion and coating properties (Figure 4). Unlike natural melanin, they are free of proteins, which can potentially hinder functional device applications of melanin[17,20].

Recently, melanin films are demonstrated by the electrochemical deposition of DHI precursors in a tris-hydroxymethyl-aminomethane (THAM) buffer solution by constant potential method[21]. Similarly, polydopamine films are electrochemically deposited from dopamine by the cyclic voltammetry method[22](Figure 6). Using other precursors such as 5,6-dimethoxyindole-2-carboxylic acid (DMICA), melanin film could be fabricated on a conductive substrate by constant current method[23].

3. Functional Properties of Melanin

3.1. Optical properties

Melanin has interesting light absorption characteristics. Even though natural melanin and synthetic melanin have different chemical structures, both present a monotonous decrease of the absorption coefficient vs. λ without marked absorption bands in the UV, visible, and near IR ranges[5,24](Figure 8). M. A. Rosei et al. proposed that this characteristic shape is originated from a disordered structure of melanin, which is composed of elementary nano-sized two-dimensional clusters packed into stacks[25]. According to this model, π-π* electron transitions occur inside nano-sized clusters by absorbing broad range energy, and that is the reason of the absorption spectrum of melanin[4].

3.2. Electrical properties

Melanin, particularly eumelanin, has electrical conductivity because they have π-π conjugated backbone structures (Figures 7, 9). In 1970s, eumel-
Figure 7. Melanin structures and functional groups and their resulting properties[1].

Figure 8. UV-Visible absorbance of (a) natural and (b) synthetic melanin solutions[5].

Figure 9. Electrical conductivity of natural (a) and synthetic (b) melanin before and after heat treatment[11].

Figure 10. (A) Conductivity of melanin as a function of water content. (B) Scheme of the comproportionation reaction[26].

Figure 11. Schwann cells growth dynamics on a melanin film[12].

3.3. Biocompatibility

A natural polymer, melanin, is thought to be inherently biocompatible and biodegradable. Christopher J. Bettinger et al. tested in vitro biocompatibility of melanin films by using Schwann cells (SCs) and PC12 neural cells, and in vivo biocompatibility by implanting melanin films in a mouse[12]. In Figure 11, the SCs cultured on a melanin substrate grew rapidly and exhibited more activated phenotype than the cells cultured on a collagen substrate, positive control, and on an un
coated substrate, negative control. In Figure 12, biocompatibility of melanin was also proved by in vivo PC12 cell growth rate and its neurite length in the presence of nerve growth factor (NGF). In Figure 13 shows that while silicone implants were encapsulated by severe inflammatory reaction, melanin implants were simply fractured by mechanical rupturing and were gradually degraded in a peripheral nerve.

This in vivo response of nerve to melanin implants implies that melanin is a promising candidate for biodegradable coatings as well as biocompatible functional materials. Dan kai et al. demonstrated electrically conductive melanin composite nanofibers by mixing melanin, gelatin, and poly (L-lactide-co-ε-caprolactone) (PLCL). They also cultured Human cardiac myocytes (HCM) on the conductive melanin nanofiber scaffolds to test regenerative cardiac functions. While mechanical modulus decreased by adding melanin, melanin containing fibers showed improved expression of cardiac-specific proteins and enhanced cell proliferation[29]. The result implies that the concentration of melanin is not just biocompatible, but also facilitates regenerative

tissue functions, particularly for electrogenetic cells. Others also demonstrated mammalian cell biocompatibility of graphene - melanin composites in order to increase electrical conductivities and biodegradability of melanosome, melanin materials[30,31].

3.4. Other properties

Metal ion binding: Melanin can bind to metal ions such as Ca\(^{2+}\), Mg\(^{2+}\), and Zn\(^{2+}\) with o-benzosemiquinone, o-benzosemiquinone, cis-semidiones, and flavin semiquinones in melanin structures (Figure 14). In 1978, C. C. Felix et al. reported that this metal chelating function of melanin by free radical concentration by Electron Spin Resonance (ESR) measurement[1,14]. In addition, Da Jeong Kim et al. investigated the binding capacity of heavy metal ions to synthetic melanin particles (Figure 15). After synthesizing melanin particles by oxidative polymerization of DOPA, heavy metals such as lead, copper,
and cadmium ions were adsorbed on the synthesized melanin particles. The synthetic melanin particle shows excellent binding capacities due to the high surface volume of the particles in solution[32].

Radical scavenging Malgorzata Rozanowska et al. used a pulse radiolysis technique for detecting radical scavenging property of melanin. Their results show that melanin can act as both oxidizing radical scavenger and deducing radical scavenger[13]. This strong anti-oxidation properties suggest melanin to be anti-oxidant additives[33,34].

4. Applications of Melanin

4.1. Sensors

Macro Araujo et al. made pH-responsive drug release devices by using Sepia officinalis ink. By changing pH, structural conformations of melanin are rearranged because DHI and DHICA monomers, having carboxylic acid (pKa ≒ 4.5) and phenolic group (pKa ≒ 9) respectively, are directly responsible for the chemical and surface physical properties[35]. Furthermore, melanin film was used as a pH sensor of an extended gate field effect transistor (EGFET) by Marina Piacenti da Silva et al.[36]. The two hydroxyl groups in DHICA, quinone imine and hydroxyl group of carboxylic acid[37], act as potential binding sites for H⁺ ions. These bindings make a melanin film as the active layer in EGFET pH sensors with good sensitivity. Tong-Fei Wu et al. also reported the water-soluble dopamine-melanin films for the applications of ultra-sensitive and ultra-fast humidity sensors[38](Figure 16). Maria D. Rubianes et al. used carbon nanotubes paste electrodes (CNTPE) and modified the electrodes with melanin to detect dopamine quantitatively in presence of high excess of ascorbic acid[39].

4.2. Batteries

Young Jo Kim et al. fabricated melanin electrodes with PTFE, extracted from Sepia officinalis, as sodium-ion energy storage devices utilizing the ability to form homogeneous nano-particles and the conductivities by hydration-dependent hybrid electronic-ionic carriers. Due to the low energy density compared to inorganic nano-particles, melanin anode needs to be improved by altering the chemical functionality of protomolecules and by increasing the surface areas for maximizing the specific sodium-ion loading capacity. This demonstrates the potential use of melanin anode[23]. In addition, they suggested the possible uses of eumelanin half-cell of reversible Mg²⁺ ion charge-discharge, by utilizing the structural stability of melanin in water and their relatively high density of catechol groups[40](Figure 17).

4.3. Other applications

Weifu Dong et al. reported the poly(vinyl alcohol) (PVA) / melanin composites with enhanced thermal stability above pure PVA (Figure 18). Compared with natural melanin, synthetic melanin obtained from oxidation of dopamine exhibited higher efficiency on increasing the decomposition onset temperature by 80-110 °C. By addition of synthetic
natural, the low-temperature mass loss on the first step of PVA was disappeared and the decomposition onset temperature was shifted to 310-340 °C[41]. Recently, Ming Xiao and Tong-Fei Wu et al. fabricated the melanin films, which show the bio-inspired structural coloration by self-assembly of synthetic melanin nanoparticles (Figure 19). Reflective colors were controlled by the change of film thickness. Green and red color were shown at 338 ± 9 and 444 ± 15 nm in thickness, respectively[42,43].

5. Conclusion

This mini-review provides an overview of recent findings including the synthesis and molecular structures of melanin, their multifunctionalities such as optical, electrical, and biocompatible properties. Although their uses in the real world are still in the stage of emerging embryo, the device applications of multifunctional melanin will be actively expanded such as from sensors to biomedical implants.

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