Melanin biosynthesis in bacteria, regulation and production perspectives

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Received: 24 September 2019 / Revised: 25 October 2019 / Accepted: 4 November 2019 / Published online: 7 December 2019 © Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract
The production of black pigments in bacteria was discovered more than a century ago and related to tyrosine metabolism. However, their diverse biological roles and the control of melanin synthesis in different bacteria have only recently been investigated. The broad distribution of these pigments suggests that they have an important role in a variety of organisms. Melanins protect microorganisms from many environmental stress conditions, ranging from ultraviolet radiation and toxic heavy metals to oxidative stress. Melanins can also affect bacterial interactions with other organisms and are important in pathogenesis and survival in many environments. Bacteria produce several types of melanin through dedicated pathways or as a result of enzymatic imbalances in altered metabolic routes. The control of the melanin synthesis in bacteria involves metabolic and transcriptional regulation, but many aspects remain still largely unknown. The diverse properties of melanins have spurred a large number of applications, and recent efforts have been done to produce the pigment at biotechnologically relevant scales.

Keywords Melanin · Biopolymer · Biomaterial · L-DOPA · Homogentisate · Melanin synthesis control · Stress protection

Introduction
The production of dark bacterial pigments related to tyrosine metabolism was discovered more than a century ago (Beijerinck 1900; Beijerinck 1911; Skinner 1938), but many aspects have not yet been completely elucidated. The term “melaina” (from Greek μέλας black and ἀεί always, meaning “always black matter”), from which the word melanin derives, was first coined by Bizio 1 to name the black matter he extract-

1 Bartolomeo Bizio was an Italian scientist, one of the precursors of modern microbiology though little is known about him at present. He chemically analyzed the ink of Sepia that he considered of a unique and admirable black color. In words of Bizio “having obtained a black matter so pure and so special that it cannot be compared with any of the known substances, I felt compelled to call it with a name that belonged only to it, naming her melaina” (Bizio 1825).

ed from the ink of the cuttlefish Sepia (Bizio 1825; Berzelius 1840). Melanins are heterogeneous pigments formed by the oxidative polymerization of indolic or phenolic compounds, found in many animals, plants, and some fungi and bacteria (Solano 2014; Toledo et al. 2017). The broad distribution of melamins suggests that they have an important role in many organisms. These biopolymers are classified into different types taking into account their chemical nature, the synthesis pathways, and the particular enzymes involved. Studies performed in recent years dealing both with the remarkable properties of melanins and their functions in diverse environments inspire innovative applications, such as the development of functionalized biomaterials, by combining melanin with metals or other biopolymers. Development of processes to produce environmentally friendly and cost-effective melanins using microorganisms would pave the way for future applications for these interesting pigments.

The general aspects of melanin chemical nature and biosynthesis have been reviewed by Plonka and Grabacka (2006) and Solano (2014). This review will focus on the biosynthesis of bacterial melanins with emphasis on regulatory aspects, the role of these polymers on bacterial ecology and physiology, and the biotechnological production of these pigments.

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Chemical characterization of bacterial melanins

Melanins are formed through the oxidation of hydroxylated aromatic compounds giving rise to reactive quinones that then polymerize forming these heteropolymeric pigments in the presence of oxygen (Fig. 1). Tests used to determine whether black-brown pigments produced by microorganisms are melanins take into account their insolubility in most organic solvents and water, bleaching by oxidizing agents and precipitation with ferric chloride (Sajjan et al. 2010; Mekala et al. 2019). Melanins cannot be described in terms of a single well-defined structure and their poor solubility severely limits the range of techniques that can be used to determine their chemical characteristics.

Melanins are routinely analyzed by UV-visible and IR spectroscopy. All types of melanin have similar UV-visible spectra with highest absorption at the UV region of 200 to 350 nm, with a continuous decrease in the absorbance towards the visible region (Mekala et al. 2019). This conserved characteristic is attributed to the complex structure of melanins (Tarangini and Mishra 2013). As the decrease in the absorbance with increasing wavelength is almost linear for melanins, the slope of log absorbance versus wavelength from 400 to 600 nm was recently used to identify these pigments (Manivasagan et al. 2013; Li et al. 2018). Characterization of melanins through FTIR (Fourier transform infrared) spectroscopy provides information on functional groups, revealing strong similarities between different kinds of natural melanins and synthetic DOPA melanin (Sajjan et al. 2010; Drewnowska et al. 2015; Mekala et al. 2019). Other specific additional analysis can be performed to obtain a more exhaustive characterization of the polymer (Gómez-Marín and Sánchez 2010; Ganesh et al. 2013; Guo et al. 2014; Banerjee et al. 2014; El-Naggar and El-Ewasy 2017).

Melanin biosynthesis

Most bacterial melanins are formed due to transformations of aromatic amino acids such as tyrosine. Additionally, some bacteria can produce melanin from malonyl-CoA in a process catalyzed by polyketide synthases (Fig. 1).

Melanin synthesis through type III polyketide synthases was thought to be exclusive to plants until it was described in Streptomyces griseus in 1999 (Funa et al. 1999). This pathway involves the sequential decarboxylative condensation of five molecules of malonyl-coenzyme A catalyzed by the homodimeric type III polyketide synthase RppA leading to the synthesis of 1,3,6,8-tetrahydroxynaphthalene (THN). A member of the cytochrome P450 family co-transcribed with rppA catalyzes the oxidative dimerization of two THN subunits to yield hexahydroxyperylenequinone (HPQ) (Funa et al. 2005). The autopolymerization of this unstable precursor leads to the formation of brownish HPQ melanin (Fig. 1).

The most widespread pathways for melanin synthesis in bacteria involve melanin precursors derived from tyrosine transformations. This monohydroxylated compound is oxidized to yield dihydroxylated (diphenol) derivatives through reactions in which the amino group can be conserved, giving

Fig. 1 Schematic representation of melanin production in bacteria, indicating key chemical transformations common to bacterial melanin forming processes. Malonyl-CoA and tyrosine, the two compounds shown at the top, are involved in different melanin biosynthesis pathways. 4-HPA, 4-hydroxyphenylacetate; 4-HPP, 4-hydroxyphenylpyruvate; THN, 1,3,6,8-tetrahydroxynaphthalene; L-DOPA, L-3,4-dihydroxyphenylalanine; HMG, homogentisate (2,5-hydroxyphenylacetate); HPC, homoprotocatechuate (3,4-hydroxyphenylacetate); HPQ, 1,4,6,7,9,12-hexahydroxyperylene-3,10-quinone

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rise to L-DOPA (L-3,4-dihydroxyphenylalanine), or eliminated prior to oxidation, generating compounds such as homogentisate (2,5-dihydroxyphenylacetate) or homoprotocatechuate (3,4-dihydroxymandelate). These compounds are oxidized spontaneously or through the activity of specific enzymes giving rise to dopaquinones or benzoquinones. Melanins are the result of the autopolymerization of these quinones (Fig. 1).

DOPA melanins are synthesized by tyrosinas and laccases. The tyrosinas (EC 1.14.18.1) are bifunctional copper containing polyphenol oxidases that catalyze the hydroxylation of tyrosine to L-DOPA and its subsequent oxidation to o-dopaquinone (Claus and Decker 2006) (Fig. 1). This quinone suffers spontaneous cyclization to indole quinone, and finally, this compound or its carboxylated form spontaneously polymerize to form brown to black DOPA melanins, also known as eumelanins (Plonka and Grabacka 2006). In the presence of cysteine, L-DOPA can undergo cysteinylpolymerization prior to polymerization, originating yellow to red sulfur-containing melanins (Zaidi et al. 2014).

Tyrosinas are widely distributed in nature and can have monophenol and o-diphenol substrate specificities (Faccio et al. 2012; Fairhead and Thöny-Meyer 2012). Tyrosinas related to melanin synthesis in bacteria were initially studied in Streptomyces (Lerch and Ettinger 1972), in which they are encoded by the bicistronic operon melC. The tyrosinase MelC2 remains inactive until it is secreted and activated with the help of MelC1 that acts as a chaperone for secretion and copper incorporation into the tyrosinase active site (Leu et al. 1992). The tyrosinase, that lacks any signal peptide, is exported through the general twin-arginine translocation (Tat) pathway as a complex with MelC1, which has a typical Tat-targeting signal (Schaerlaeken et al. 2001). After transport, MelC1 dissociates from the tyrosinase. Both dissociation and tyrosinase activation depend on the presence of copper in the medium (Chen et al. 1992; Tsai and Lee 1998). The first crystal structure resolved of a tyrosinase was that of the Streptomyces castaneoglobisporus, revealing that the enzyme dinuclear Cu center is flexible and that this flexibility is important for its catalytic specificity (Matoba et al. 2006). Tyrosinas involved in the synthesis of melanin are present in Gram-positive and Gram-negative bacteria, such as Sinorhizobium meliloti (Castro-Sowinski et al. 2002), Bacillus subtilis (Castro-Sowinski et al. 2002), and Alteromonas sp. (Sanchez-Amat and Solano 1997), and Bacillus sp. (Dalfard et al. 2006). The production of another kind of melanin synthesized by polyphenol oxidases from catechol in some strains of Azotobacter chroococcum has been proposed to occur in nitrogen fixing conditions in the presence of oxygen (Shivprasad and Page 1989; Herter et al. 2011).

Originally, synthesis of melanin in bacteria was thought to occur only through the DOPA pathway. In 1972, a brown pigment derived from homogentisate was described in Pseudomonas aeruginosa and was called pyomelanin (Yabuuchi and Ohyama 1972). Two decades later, it was found that the 4-hydroxyphenylpyruvate dioxygenase directed the production of a pigment derived from homogentisate in Streptomyces avermitilis (Denoya et al. 1994). This kind of pigment was known to be produced from oxidative degradation of tyrosine and found in the urine of alkaptonuric patients. In fact, alkaptonuria was the first human disorder, described by Garrod in 1902, found to conform the principles of the Mendelian recessive inheritance (Garrod 1996; Mistry et al. 2013). Although the homogentisate pathway is common to virtually all forms of life, from animals and plants to fungi and bacteria, it does not occur in the model organism E. coli (McFall and Newman 1996) and was largely overlooked in bacteria until recent studies performed mostly in Pseudomonas (Arias-Barrau et al. 2004; Rodriguez-Rojas et al. 2009).

In the homogentisate pathway, tyrosine is catabolized in five successive steps. First, tyrosine is deaminated into 4-hydroxyphenylpyruvate by aromatic amino acid aminotransferases. The 4-hydroxyphenylpyruvate dioxygenase (EC 1.13.11.27) acts on this compound to generate homogentisate in a complex reaction that involves oxygen addition, decarboxylation, and rearrangement of the side chain on the aromatic ring (He and Moran 2009).
Homogentisate is then degraded by the homogentisate 1,2-dioxygenase and successive enzymes with fumarate and acetooacetate as final products. The accumulation, spontaneous autooxidation, and polymerization of homogentisate lead to the synthesis of melanin (Fig. 1). This accumulation can be due to the absence or inactivation of the homogentisate 1,2-dioxygenase or to increased 4-hydroxyphenylpyruvate dioxygenase activity. Melanin-producing Aeromonas contain different mutations in the homogentisate 1,2-dioxygenase gene (hmgA). For example, in A. salmonicida A449, hmgA is a pseudogene, while in A. salmonicida subsp. pectinolytica 34mel T and A. media WS, this gene is interrupted by transposases (Pavan et al. 2015; Wang et al. 2015). In contrast, Vibrio cholerae HTX-3, Shewanella colwelliana D, and a strain of Hyphomonas accumulate homogentisate due to increased amounts of the 4-hydroxyphenylpyruvate dioxygenase and not to a mutation in hmgA (Kotob et al. 1995). Additionally, homogentisate accumulation and melanin formation was observed in V. cholerae strains that display a 15-bp deletion in hmgA (Wang et al. 2011), and a single amino acid substitution (G378R) in the homogentisate 1,2-dioxygenase is responsible for pigmentation in Burkholderia cepacia complex (Gonyar et al. 2015). Transposon insertions in hmgA also resulted in accumulation of homogentisate and production of mel in clinical isolates of Pseudomonas aeruginosa (Rodriguez-Rojas et al. 2009). In the photosynthetic Rubrivivax benzoativic, accumulation of melanin was found to be due to the absence of hmgA (Mekala et al. 2019). Other bacterial genera with some strains capable of producing homogentisate melanins are Xanthomonas campestris pv. phaseoli (Goodwin and Sopher 1994), Klebsiella pneumoniae, Alcaligenes faecalis, and Enterobacter sp. (Singh et al. 2018).

Another pathway reported for the synthesis of tyrosine-derived melanins involves the oxidation and polymerization of homoprotocatechuic acid, an isomer of homogentisate (Fig. 1). The formation of a dark brown pigment in Serratia marcescens was attributed to the 4-hydroxyphenylacetate 3-monooxygenase activity (EC 1.14.14.9). This enzyme can catalyze the hydroxylation of 4-hydroxyphenylacetate to 3,4-dihydroxyphenylacetate (homoprotocatechuate), so it has been proposed that pigment formation was related to accumulation of this compound (Trias et al. 1989; Gibello et al. 1995). However, this enzyme catalyzes the oxidation of dihydroxylated aromatic compounds giving rise to quinones has relaxed enzyme specificity (Gibello et al. 1997), and the chemical nature of the pigment formed in S. marcescens could not be determined, so it cannot be ruled out that it could arise from the oxidation of other dihydroxylated compounds.

**Control of melanin synthesis in bacteria**

There are many different pathways for melanin synthesis, but all involve the oxidation of hydroxylated aromatic compounds. Some of these compounds are synthesized by tyrosinases, laccases, or polyketide synthases in dedicated biosynthetic pathways, subject to specific regulation. Other hydroxylated aromatic compounds are intermediates in catabolic pathways, such as the degradation of tyrosine, and can accumulate as a result of imbalances or interruptions in the degradation pathways (Fig. 2).

In bacteria that produce melanin through the oxidation of L-DOPA, pigment formation is linked to the regulation of enzyme synthesis driven by nutrient factors such as the presence of Cu, nitrogen sources, and oxygen availability, but also by general regulatory networks, like those that control cellular processes such as nitrogen fixation, stress responses, or morphogenesis.

Melanin formation has been extensively studied in rhizobia, in which pigmentation was observed to depend on multiple nutritional factors. For example, in Rhizobium leguminosarum bv. phaseoli, in which melanin-related genes are found in the symbiosis plasmid, melanin is formed in rich...
medium but not in minimal medium even when both tyrosine and Cu are added (Borthakur et al. 1987). Regulation of melanin synthesis in this microorganism depends on the regulator of nitrogen fixation NifA that activates the transcription of the tyrosinase coding gene, especially at low oxygen availability (Hawkins and Johnston 1988). A study of melanin-deficient Sinorhizobium meliloti transposon mutants revealed a relationship between a thioredoxin and melanin production. The gene coding for the thioredoxin (trxL) is induced in melanin-producing conditions, and trxL mutants are unable to produce pigment due to a greatly diminished tyrosinase activity (Castro-Sowinski et al. 2007). The thioredoxin also affects nitrogen fixation, and it has been proposed to modulate the redox potential (Castro-Sowinski et al. 2007), providing a possible link between oxygen availability, nitrogen fixation, and melanin production in S. meliloti.

The presence of some amino acids, and particularly methionine, was observed to increase the transcription of the tyrosinase gene in several Streptomyces (Cramer et al. 1982; Ikeda et al. 1996; Katz and Betancourt 1988). Interestingly, tyrosine, the tyrosinase substrate, was not observed to increase its activity, and in S. castaneoglobisporus even had small inhibitory effect on tyrosinase activity (Ikeda et al. 1996). In Streptomyces michiganensis, supplementation of the medium with ammonium, but not other nitrogen sources such as KNO₃, urea, or amino acids, inhibited tyrosinase formation at the transcriptional level (Held and Kutzner 1990). The role of Cu in melanization has been extensively studied in Streptomyces, in which it is necessary for tyrosinase activity and increases the transcription of the corresponding gene (Held and Kutzner 1990). Although Cu has been observed to enhance melanin formation in most cases, other metals can have a similar effect. A recent detailed analysis of nutritional factors that affect pigmentation in a Streptomyces isolate reported that peptone, but not tyrosine, increased tyrosinase activity, and that the addition of Fe and Ni have a strong enhancing effect on tyrosinase expression and melanin production (Wang et al. 2019).

In some cases, melanin formation is induced by different kinds of stress. Pigmentation is induced by stress conditions in M. mediterranea, such as those encountered when they reach the stationary phase, suggesting that melanin synthesis could be part of the adaptive response in this microorganism (Lucas-Elío et al. 2002). In Azospirillum, exposure to Zn triggers pigment production followed by encystation (Gowri and Srivastava 1996). The induction of melanin formation at high temperatures was observed in B. thuringiensis (Ruan et al. 2004), that produces a thermostable tyrosinase (Liu et al. 2004).

In several Streptomyces species, tyrosinase expression is activated by the transcriptional regulator AdpA, that controls morphological development in response to A factor levels (Zhu et al. 2005). AdpA also regulates the synthesis of the type III polyketide synthase RppA, responsible for HPQ melanin formation. This transcriptional regulator, along with the stress response sigma factors, activates the transcription of rppA, and of many genes required for both morphological development and secondary metabolism (Takano et al. 2007). These results show a clear regulatory link between pigment formation and other processes such as sporulation in these physiologically and morphologically complex bacteria.

Unlike the cases in which melamins are synthesized by dedicated biosynthetic pathways, melanin formation from degradation intermediates such as homogentisate depends on the accumulation of these compounds due to alterations in the corresponding degradation routes (Fig. 2). The homogentisate pathway involves enzymes that lead to the formation of 4-hydroxyphenylpyruvate (4-HPP) from phenylalanine (PhhA and PhhB), or tyrosine (PhhC/TyrB) followed by the conversion of 4-HPP to homogentisate (catalyzed by Hpd), that is further degraded by HmgA to acetoacetate and fumarate. The transcription of the corresponding genes is normally controlled by the concentration of aromatic amino acids. In Pseudomonas, the transcriptional regulator PhhR activates phhA, hpd, and hmgA in the presence of phenylalanine or tyrosine (Herrera et al. 2009; Palmer et al. 2010), while HmgR represses hmgA in P. putida (Arias-Barrau et al. 2004). An in silico study has proposed that HmgR could also control hpd in Shewanella (Stepanova and Rodionov 2011), while in S. meliloti hpd is activated by the specific regulator HpdR (Loprasert et al. 2007).

Accumulation of homogentisate can be caused by an increase in the expression of Hpd, that converts 4-hydroxyphenylpyruvate to homogentisate (Kotob et al. 1995), by the absence of HmgA (Mistry et al. 2013), the enzyme that leads to homogentisate degradation, or by a decreased activity of this last enzyme (Sanchez-Amat et al. 1998) (Fig. 2). Differences in the expression of the genes that code for these enzymes indicate that other factors, apart from aromatic amino acid availability, can affect their synthesis. Mutant studies performed in A. media, P. aeruginosa, and R. solanacearum have revealed that many genes, including several transcriptional regulators and transport proteins that are not directly involved in the formation or degradation of homogentisate, can affect melanin biosynthesis (Hunter and Newman 2010; Wang et al. 2015; Ahmad et al. 2016). Nutritional factors, but also physicochemical conditions and growth mode, can affect melanization. In A. salmonicida subsp. pectinolytica, the presence of glycerol was observed to abolish melanin synthesis through a combination of metabolic and regulatory effects, including the generation of a more reduced environment, unfavorable for homogentisate oxidation, and a significant inhibition of hpd transcription (Pavan et al. 2019).
High temperature and biofilm formation promoted melanin synthesis in *Pseudoalteromonas*, since these conditions induced the synthesis of the enzyme leading to homogenisate formation more than the one leading to its degradation, resulting in pigment formation (Zeng et al. 2017a). In *V. cholerae*, hyperosmotic stress and high temperatures increased melanin formation, especially in nutrient poor growth media (Coyne and Al-Harthi 1992), and in *Vibrio anguillarum*, a Lux-R like transcriptional regulator controls biofilm formation and pigment production (Croxatto et al. 2002), providing further evidence of the relationship between biofilm and melanin formation. In *R. solanacearum* that produces melanin in stationary phase when grown in minimal medium with tyrosine, several transcriptional regulators were shown to control melanin production. While OxyR, RpoS, and HrpG, involved in the regulation of stress response and pathogenicity, are essential for melanin synthesis (Ahmad et al. 2016), another transcription factor represses pigment formation in this microorganism (Ahmad et al. 2017). Factors that affect melanin synthesis are multiple and diverse, as shown by a recent study in which a *P. aeruginosa* transcription factor expressed in response to exposure to surface acoustic waves increased melanin formation through an unknown mechanism (Ben-David et al. 2018).

The diversity of melanin synthesis pathways and factors that affect pigmentation shows that this process is subject to several types of control, even in bacteria that produce the pigment through an apparently non-dedicated pathway. In spite of differences observed in the factors that affect melanization in different organisms, in most bacteria, both the presence of tyrosine and Cu have been observed to enhance melanogenesis. In the case of DOPA melanins, this effect can be obviously attributed to the fact that tyrosinases contain this metal in their structure. However, the underlying causes of the enhancing effect of Cu on melanogenesis is not straightforward in the case of bacteria that accumulate other melanins that do not involve tyrosinases or other known Cu-containing enzymes.

### Ecological and physiological role of bacterial melanins

Melanins can have a wide variety of functions in different bacteria. In both pathogenic and environmental bacteria, melanins confer adaptive advantages, increasing fitness and survival in many stress conditions (Fig. 3).

The relationship between melanin synthesis and the increase of virulence has been extensively reported in bacterial pathogens (Nosanchuk and Casadevall 2003; Plonka and Grabacka 2006). Melanin can increase microbial virulence through two mechanisms: it reduces the susceptibility of the pathogen to host defense mechanisms and affects the host immune response to infection (Nosanchuk and Casadevall 2006). In melanogenic *V. cholerae*, pigment production increases cholera toxin and pilus expression, and enhances host colonization (Valeri et al. 2009). Due to its free radical scavenging potential, melanin can diminish host cell oxidative burst as observed in some melanin producing epidemic strains of *B. cenocepacia*, protecting this pathogen from oxidative stress (Keith et al. 2007). This trait was also observed for the plant pathogen *R. solanacearum*, and it has been suggested that protection against oxidative stress could help the bacteria cope with plant defense mechanisms (Ahmad et al. 2016). In *Legionella pneumophila*, melanin is involved in the increase of iron bioavailability through the reduction of ferric to ferrous form, stimulating bacterial growth under iron-limited conditions such as those encountered in mammalian hosts and natural environments (Zheng et al. 2013). During chronic *P. aeruginosa* infections in humans, melanin producers emerge spontaneously due to deletions in a genomic region containing *hmgA*. This phenomenon that leads to mixed populations of pigmented and non-pigmented bacteria in continuous evolution has been attributed to selective pressure exerted by intraspecific competition (Hocquet et al. 2016).

In non-pathogenic bacteria, melanin is related to several biological interkingdom interactions (Fig. 3). During symbiosis of *Rhizobium etli*, tyrosinase activity, and consequently melanin production, is necessary during the first stages of nodulation, when bacteria need to cope with reactive oxygen species (ROS) and phenolic compounds derived from plant defenses (Piñero et al. 2007). Melanin is also involved in interactions between bacterial biofilms and other organisms. The biofilms of the marine bacterium *Pseudoalteromonas lipolytica* secrete melanin that inhibits the larval settlement and metamorphosis of mussels leading to reduced biofouling (Ocampo et al. 2017). Melanin production in *V. cholerae* biofilms increases ROS production, protecting this microorganism against amoeba predation (Noorian et al. 2017).

One of the major roles traditionally attributed to melanins is their capability to protect cells from UV radiation. In *Bacillus anthracis*, pigmented mutants are more resistant to UV exposure (Han et al. 2015), and melanized spores of *S. griseus* are more resistant to UV irradiation than colorless mutants (Funa et al. 2005). In addition, melanogenic *P. aeruginosa* strains are more tolerant to photodynamically induced oxidative stress (Orlandi et al. 2015). While bacterial melanin protects the producing organisms from photodamage, this protection can be extended to other organisms living in close association. For example, the dark pigmentation of sponges that contain *Vibrio, Providencia*, and *Shewanella* symbionts is due to melanins secreted by these melanogenic microorganisms that protect sponge cells from photodamage (Vijayan et al. 2017). The fact that several non-phylogenetically related bacteria sharing the same ecological niche produce melanins suggests that these pigments have an important role in nature.
Melanin production can also provide selective advantages for the survival in many environments, in some cases by enhancing the capability to respond to rapidly changing environmental conditions. Melanogenic members of *Shewanella* can span from anoxic to highly oxygenated zones. In these bacteria, melanin can be utilized as terminal electron acceptor for anaerobic respiration and also as electron shuttle during respiration of Fe(III) minerals when oxygen concentration declines, thus conferring a competitive advantage by enhancing respiratory versatility (Turick et al. 2002; Turick et al. 2009). Melanogenic bacteria have also been found in extreme environments. Some examples are *Streptomyces cyaneofuscatus*, that has a highly thermoresistant tyrosinase, isolated from the Sahara desert (Harir et al. 2018), the psychrotolerant melanin producer *B. weihenstephanensis* isolated from cold environments in Poland (Drewnowska et al. 2015), or *Lysobacter oligotrophicus*, a bacterium able to increase melanin production after UV exposure, isolated in Antarctica (Kimura et al. 2015). Highly contaminated areas are also extreme environments where microorganisms have to thrive under harsh conditions of anthropogenic origin such as those containing nuclear waste, heavy metals, or oil spills. Melanin production in *A. salmonicida* subsp. *pectinolytica*, isolated from a heavily polluted river (Pavan et al. 2000), has been proposed to help this extremophile cope with the high concentrations of heavy metals, hydrocarbons, and other pollutants found in this environment (Pavan et al. 2015).

**Biotechnological applications**

The diverse and unusual properties of melanins make them useful for a variety of applications (Fig. 3). Due to its photoprotective, antioxidant, and antimicrobial features, melanin can have cosmetic and pharmaceutical uses. For example, melanin produced by *Pseudomonas stutzeri* was used to increase the sun protection factor of commercial sunscreens (Kurian and Bhat 2018). In addition, these pigments might have clinical and agricultural applications. Melanin obtained from *Pseudomonas balearica*, isolated from a marine green alga, has been proposed as a biocontrol agent because of its antimicrobial activity against *Staphylococcus aureus, E. coli, Candida albicans*, and the phytopathogenic *Erwinia* (Zerrad et al. 2014). Another interesting application concerns the insecticidal crystal proteins produced by *B. thuringiensis*. A melanin producer mutant of this bacterium protected the protein from UV radiation damage, indicating that it could be

![Fig. 3 Ecological and physiological role of melanin and derived applications](image-url)
useful for the industrial production of light-stable environmentally friendly insecticides (Liu et al. 2013).

Melanogenic bacteria can be used for bioremediation purposes due to the metal affinity and high adsorption capacity of melanins. For example, in situ stimulation of melanin synthesis by indigenous microbes through addition of tyrosine increased uranium immobilization in contaminated soils (Turick et al. 2008). Different studies proposed the detoxification of soils or waters polluted with heavy metals by melanin producing microorganisms as _A. chroococcum_ (Rizvi et al. 2019) or by melanin nanoparticles produced by _P. stutzeri_ (Thaira et al. 2019; Manirethan et al. 2018), during environmental management. A recombinant _E. coli_ with membrane bound tyrosinase, that resulted in the formation of an outer melanin layer, was used for the bioremediation of drug pollution in wastewaters in a bioreactor assay, and the melanin could be regenerated after chemical compounds adsorption (Gustavsson et al. 2016).

In addition, melanins are considered disordered organic conductors, with unique physical and chemical properties, with the potential to be used in different technological applications (Gómez-Marín and Sánchez 2010). The ability of melanin to function as an electron shuttle from the cell to iron minerals in _Shewanella oneidensis_ allows electron transfer to electrodes, enhancing electricity production in microbial fuel cells (Turick et al. 2010).

Some recent studies reveal the potential of melanins in innovative nanotechnology applications: the synthesis of crystalline, flexible, and thermostable nanomelanin-polyhydroxybutyrate nanocomposite films for use in biomedicine or as packaging material (Kiran et al. 2017); the environmentally gentle synthesis and/or stabilization of Ag, Au, Pt, Cu, Mn, and Ni nanoparticles mediated by melanins from _Actinoalloteichus kathirae_ (Surwase et al. 2013). To reduce melanin production costs, fruit waste extracts were used as economical carbon source using a soil isolate of _Bacillus safensis_ (Tarangini and Mishra 2014).

Some strategies focused on the isolation of melanin producing bacteria from marine environments. Thus, Kiran et al. (2017) optimized melanin production using a strain of _Pseudomonas_ isolated from a marine sponge. The melanin obtained was readily soluble in hexane, DMSO, and water at pH above 7, and used to develop nanomelanin particles used to synthesize non-toxic nanomelanin-PHB (polyhydroxybutyrate) nanocomposite films. _Pseudomonas stutzeri_ HMGM-7, isolated from the surface of a red seaweed, was used to produce melanin in nutrient broth cultures prepared in sea-water and supplemented with tyrosine, and purified through an easy and inexpensive two-step procedure consisting of a simple acid precipitation followed by centrifugation (Ganesh Kumar et al. 2013).

_Nocardiopsis alba_ MSA10 melanin, produced in sucrose-containing culture medium, was used for the environmentally gentle synthesis of silver nanostructures. Melanin supernatants were first adjusted to pH 9 with NaOH to ensure complete polymerization previous to acid precipitation. The purified melanin proved to be stable in a wide range of pHs, temperatures up to 100 °C even for 3 h, and different sources of light including UV (Kiran et al. 2014).

Studies involving other microorganisms, such as _Actinoalloteichus_ sp. MA-32 (Manivasagan et al. 2013) or _Streptomyces glaucescens_ NEAE-H (El-Naggar and El-Ewasy 2017), could not achieve melanin yields suitable for industrial production even after medium optimization (Table 1).

Production of melanin has also been studied in recombinant _E. coli_ expressing an improved mutant version of the _Rhizobium etli_ tyrosinase using two tyrosine feeding steps (Lagunas-Muñoz et al. 2006). A different strategy, that combined strain manipulation and process optimization, was to express this mutant tyrosinase in _E. coli_ strains lacking the sugar phosphotransferase system and the repressor TyrR, with the idea to direct the carbon flow into the aromatic biosynthetic pathway in a strain that could produce melanin from glucose instead of tyrosine. The addition of Cu was delayed to control the activity of the tyrosinase to avoid bacterial growth problems due to the premature depletion of intracellular tyrosine (Chávez-Béjar et al. 2013).

The gene coding the 4-hydroxyphenylpyruvate dioxygenase of _P. aeruginosa_ was also overexpressed in _E. coli_ cells that gained the ability to produce homogentisate melanin although with poor yield (Bolognese et al. 2019).

**Bioproduction**

Microorganisms could be used to produce melanin at an industrial scale in environmentally friendly, economically feasible processes. Several studies have analyzed the potential of native and recombinant bacteria for the production of melanin, focusing on optimization of bacterial production, processes, or melanin purification (Table 1).

A high melanin yield was obtained from _Streptomyces kathirae_ SC-1. Addition of yeast extract and Cu ions maximized production and 13.7 g L⁻¹ melanin could be obtained after optimization, indicating that this microorganism could be a good candidate for industrial-scale production (Guo et al. 2014) (Table 1). Melanin production was doubled when the _melC_ operon of _S. kathirae_, encoding the chaperone MelC1 and the tyrosinase MelC2, was cloned with its own promoter and overexpressed in the same microorganism (Guo et al. 2015). An optimized medium supplemented with tyrosine and Cu was also used to increase melanin yield using _Brevundimonas_ sp. SGJ (Surwase et al. 2013). To reduce melanin production costs, fruit waste extracts were used as economical carbon source using a soil isolate of _Bacillus safensis_ (Tarangini and Mishra 2014).

Some strategies focused on the isolation of melanin producing bacteria from marine environments. Thus, Kiran et al. (2017) optimized melanin production using a strain of _Pseudomonas_ isolated from a marine sponge. The melanin obtained was readily soluble in hexane, DMSO, and water at pH above 7, and used to develop nanomelanin particles used to synthesize non-toxic nanomelanin-PHB (polyhydroxybutyrate) nanocomposite films. _Pseudomonas stutzeri_ HMGM-7, isolated from the surface of a red seaweed, was used to produce melanin in nutrient broth cultures prepared in sea-water and supplemented with tyrosine, and purified through an easy and inexpensive two-step procedure consisting of a simple acid precipitation followed by centrifugation (Ganesh Kumar et al. 2013).

_Nocardiopsis alba_ MSA10 melanin, produced in sucrose-containing culture medium, was used for the environmentally gentle synthesis of silver nanostructures. Melanin supernatants were first adjusted to pH 9 with NaOH to ensure complete polymerization previous to acid precipitation. The purified melanin proved to be stable in a wide range of pHs, temperatures up to 100 °C even for 3 h, and different sources of light including UV (Kiran et al. 2014).

Studies involving other microorganisms, such as _Actinoalloteichus_ sp. MA-32 (Manivasagan et al. 2013) or _Streptomyces glaucescens_ NEAE-H (El-Naggar and El-Ewasy 2017), could not achieve melanin yields suitable for industrial production even after medium optimization (Table 1).

Production of melanin has also been studied in recombinant _E. coli_ expressing an improved mutant version of the _Rhizobium etli_ tyrosinase using two tyrosine feeding steps (Lagunas-Muñoz et al. 2006). A different strategy, that combined strain manipulation and process optimization, was to express this mutant tyrosinase in _E. coli_ strains lacking the sugar phosphotransferase system and the repressor TyrR, with the idea to direct the carbon flow into the aromatic biosynthetic pathway in a strain that could produce melanin from glucose instead of tyrosine. The addition of Cu was delayed to control the activity of the tyrosinase to avoid bacterial growth problems due to the premature depletion of intracellular tyrosine (Chávez-Béjar et al. 2013).

The gene coding the 4-hydroxyphenylpyruvate dioxygenase of _P. aeruginosa_ was also overexpressed in _E. coli_ cells that gained the ability to produce homogentisate melanin although with poor yield (Bolognese et al. 2019).
Table 1  Studies focused on optimization of bacterial melanin production

| Microorganism                        | Melanin yield g l⁻¹ | Melanin type   | Tyr added | Metal ion added | Substrates                          | Time | Optimization                        | Reference                      |
|--------------------------------------|----------------------|----------------|-----------|----------------|-------------------------------------|------|-------------------------------------|--------------------------------|
| Streptomyces kathirae                | 28.8                 | DOPA melanin   | yes       | Cu             | amylopectin extract yeast extract    | 2-5 d| Recombinant                         | Guo et al. 2015                |
| Streptomyces kathirae SC-1           | 13.7                 | DOPA melanin   | yes       | Cu             | amylopectin extract yeast extract    | 2-5 d| PBD CCD                             | Guo et al. 2014                |
| Pseudomonas sp. WH001 55             | 7.6                  | DOPA melanin   | no        | no             | starch yeast extract                 | 6 d  | one-factor-at-a-time                | Kiran et al. 2017              |
| Pseudomonas stutzeri HMGM-7          | 6.7                  | DOPA melanin   | no        | none           | nutrient broth in seawater           | 3 d  | one-factor-at-a-time                | Ganesh Kumar et al. 2013       |
| Bacillus safensis                    | 6.9                  | nd             | no        | no             | fruit waste extracts                | 24 h | TD CCD                              | Tarangini and Mishra 2014       |
| Brevundimonas sp. SGJ                | 6.8                  | DOPA melanin   | yes       | Cu             | tryptone                            | 54 h | PBD CCD                             | Surwase et al. 2013            |
| *E. coli* expressing tyrosinase from *Rhizobium etli* | 6                    | DOPA melanin   | yes       | Cu             | glucose                             | 30 h | Recombinant one-factor-at-a-time    | Lagunas-Muñoz et al. 2006       |
| Streptomyces lusitanus DMZ-3         | 5.29                 | nd             | yes       | Cu             | beef extract                        | 6 d  | one-factor-at-a-time CCD            | Madhusudhan et al. 2014         |
| *S. glaucescens* NEAE-H              | 4.24                 | DOPA melanin   | no        | Ni             | soya peptone                        | 5 d  | one-factor-at-a-time CCD            | Wang et al. 2019                |
| Nocardiosis alba MSA10               | 3.4                  | nd             | yes       | Fe             | sucrose                             | 7 d  | PBD CCD                             | Kiran et al. 2014               |
| *E. coli* expressing tyrosinase from *Rhizobium etli* | 3.22                 | DOPA melanin   | no        | Cu             | glucose                             | 5 d  | Recombinant Metabolic engineering   | Chávez-Béjar et al. 2013         |
| *S. glaucescens* NEAE-H              | 0.35                 | DOPA melanin   | yes       | Fe             | protease-peptone                    | 6 d  | PBD CCD                             | El-Naggar and El-Ewasy 2017     |
| *E. coli* expressing Hpd from *Pseudomonas aeruginosa* | 0.21                 | Homogenisate melanin | yes       | nd             | glucose casamino acids              | 6 d  | one-factor-at-a-time PBD CCD        | Bolognese et al. 2019           |
| Actinoalloteichus sp. MA-32          | 0.125                | DOPA melanin   | yes       | Fe             | glycerol                            | 7 d  | one-factor-at-a-time PBD CCD        | Manivasagan et al. 2013         |

PBD Plackett-Burman design, BBD Box-Behnken design, CCD central composite design, TD Taguchi design, nd not defined
A recent report has described remarkable melanin production in bacteria isolated from sponges. *Vibrio alginolyticus* MMRF 534 and *Vibrio harveyi* MMRF 535 produce 50 and 40 g l\(^{-1}\) melanin, respectively, in marine broth without optimization, suggesting that these organisms are very good potential candidates for industrial melanin production (Vijayan et al. 2017). These results suggest that bioprospecting for melanin producing bacteria, including those associated with other organisms or thriving in extreme environments, may be useful to find melanin hyperproducers or extremozymes that could enable higher melanin yields.

Conclusions

Melanins are complex biopolymers that attract great interest due to their unusual properties and diverse biological roles. Their production in bacteria spread among different taxonomic groups, including Gram positive and Gram negative. The ability to produce different types of melanin lies in dedicated biosynthetic pathways or in enzymatic imbalances in altered metabolic routes leading to accumulation of melanin precursors. Regulation of melanin biosynthesis in bacteria depends on global and specific regulators. Understanding melanin control mechanisms could contribute to improve bioprocesses leading to melanin production, but could also be used for the control of melanogenic pathogens. The remarkable properties of these biopolymers have inspired multiple and diverse applications. In an era marked by the search for sustainable biomaterials, multifunctional melanins have not yet reached their full potential.

Acknowledgments

The authors thank Esteban Pavan for helpful comments. N.I.L. and M.J.P. are career investigators from CONICET.

Funding

This work was partially supported by the University of Buenos Aires, CONICET, and Agencia Nacional de Promoción Científica y Tecnológica.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interests.

Ethical approval

This article does not contain any studies with human or animals performed by any of the authors.

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