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REVIEW ARTICLE

Epigenetic regulation of melanogenesis in melasma

Regulação epigenética da melanogénese no melasma

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Abstract

Melasma is a chronic, multifactorial pigmentary disorder prevalent in higher skin phototypes and characterized by symmetrical facial hyperpigmentation. This narrative review analyzes the epigenetic mechanisms that regulate melanocyte activity in melasma, focusing on DNA modifications, histone alterations, and the role of non-coding RNAs (ncRNAs). The pathogenesis of the disease involves a complex interaction within the epidermal-dermal unit, influenced by ultraviolet radiation, hormonal factors, and oxidative stress. At the molecular level, melanogenesis is coordinated by the transcription factor microphthalmia-associated transcription factor, whose expression is modulated by epigenetic processes such as DNA methylation and histone acetylation (particularly H3K27ac), which alter chromatin accessibility and the transcription of key enzymes such as tyrosinase. In addition, microRNAs (miRNAs), long ncRNAs, and circular RNAs act as critical post-transcriptional regulators, even functioning as miRNA "sponges" to promote or inhibit melanin synthesis. In conclusion, understanding these epigenetic landscapes is fundamental to identifying novel biomarkers and therapeutic targets for managing the hyperpigmented phenotype in melasma.

Keywords: Melasma. Melanogenesis. Hyperpigmentation. Epigenetics. Gene expression.

Resumo

O melasma é uma doença pigmentar crónica e multifatorial, prevalente em fotótipos cutâneos mais elevados e caracterizada por hiperpigmentação facial simétrica. Esta revisão narrativa analisa os mecanismos epigenéticos que regulam a atividade dos melanócitos no melasma, centrando-se nas modificações do ADN, nas alterações das histonas e no papel dos ARNs não codificantes (ncRNAs). A patogénese da doença envolve uma interação complexa no seio da unidade epidérmico-dérmica, influenciada pela radiação ultravioleta, por fatores hormonais e pelo stress oxidativo. A nível molecular, a melanogénese é coordenada pelo fator de transcrição MITF, cuja expressão é modulada por processos epigenéticos, tais como a metilação do ADN e a acetilação das histonas (em particular H3K27ac), que alteram a acessibilidade da cromatina e a transcrição de enzimas-chave, como a tirosinase. Além disso, os microARN (miARN), os ARN longos não codificantes (ARNlnc) e os ARN circulares (ARNcirc) atuam como reguladores pós-transcricionais críticos, chegando mesmo a funcionar como "esponjas" de miARN para promover ou inibir a síntese de melanina. Em conclusão, a compreensão destes panoramas epigenéticos é fundamental para identificar novos biomarcadores e alvos terapêuticos para o tratamento do fenótipo hiperpigmentado no melasma.

Palavras-chave: Melasma. Melanogénese. Hiperpigmentação. Epigenética. Expressão génica.

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Introduction

Melasma is a chronic, treatment-resistant pigmentary disorder common in individuals with higher skin phototypes, particularly phototypes III and IV, according to the cutaneous phototype classification of the Fitzpatrick scale, created in 1976 by the American physician Thomas B. Fitzpatrick.[1] The prevalence of melasma varies significantly, being estimated between 8.8% and 40% of the population depending on ethnic composition.[2,3] This variation occurs as a function of several factors, including geographical, genetic, hormonal, and environmental aspects, as well as skin phototype. Clinically, it manifests as symmetrical reticulated hyperpigmentation and can present three predominant facial patterns: centrofacial, malar, and mandibular.[4]

At present, melasma is understood to result from a complex interaction among the constituent cells of the epidermal-dermal unit, under hormonal, genetic, and ultraviolet radiation (UVR) influence.[5] Its pathogenesis is multifactorial, involving the hyperactivity of epidermal melanocytes, as well as the participation of keratinocytes, dermal fibroblasts, mast cells, and vascular endothelial cells, alongside a persistent state of dermal inflammation and oxidative stress.[5,6] Furthermore, a direct relationship is observed between this active pigmentary disorder and photoaging; histopathologically, there is a quantitative increase in mast cells, elevated vascularization, the presence of focal basement membrane discontinuity, and a classic presentation of solar elastosis.[7]

Melasma can be classified according to the distribution of melanin across the skin layers, based on Wood's lamp examination, into epidermal, dermal, and mixed patterns.[1,8]

The organization of genomic DNA within the nucleus is dynamic and varies according to cell type and functional state, influencing chromatin accessibility and gene expression.[9-13] Epigenetic regulation encompasses molecular mechanisms that modify gene activity without altering the underlying DNA sequence, including DNA methylation, histone modifications, and non-coding RNAs (ncRNAs).[14,15] DNA methylation commonly involves the addition of a methyl group to cytosine residues within CpG-rich regions and is generally associated with transcriptional repression.[13] Histone modifications occur at specific amino acid residues and can modulate transcription by influencing chromatin remodeling and the recruitment of regulatory complexes.[16-18] ncRNAs, including microRNAs (miRNAs), represent additional regulators of gene expression and can influence cellular phenotypes through post-transcriptional mechanisms and interactions with other regulatory pathways.[19]

Despite advances in understanding the pathophysiology of melasma, the epigenetic mechanisms involved in regulating melanogenesis remain poorly understood. Histological observations have demonstrated alterations in the nuclear micromorphology of basal layer keratinocytes in areas affected by melasma, while computational analyses and volumetric quantification methods have identified changes in nuclear dimensions and chromatin organization.[20] In parallel, increased DNA methyltransferase (DNMT)1 expression and alterations in DNA methylation have been reported in malar melasma compared with unaffected skin, providing molecular evidence of epigenetic alterations associated with the disease.[21] Although these findings demonstrate that nuclear, chromatin, and DNA methylation changes occur in melasma, they do not establish a causal relationship between these alterations and the development or persistence of hyperpigmentation.[22,23]

An important unresolved question is whether epigenetic alterations represent primary mechanisms contributing to melanocyte dysfunction or secondary consequences of chronic UVR exposure, oxidative stress, inflammation, and the altered cutaneous microenvironment characteristic of melasma. The available evidence does not allow a definitive distinction between these possibilities. It is also possible that these mechanisms interact bidirectionally, whereby environmental and cellular stimuli induce epigenetic changes that subsequently influence gene expression and melanogenic activity, thereby contributing to the persistence of hyperpigmentation.

This uncertainty is particularly relevant to the potential clinical application of epigenetic findings. Although specific molecular alterations have been associated with melasma, their identification alone is insufficient to establish them as biomarkers. Reliable biomarkers would require reproducible validation in independent populations, consistent differences between lesional and non-lesional skin, and demonstrated associations with disease activity, severity, prognosis, or treatment response. Likewise, consideration of an epigenetic mechanism as a therapeutic target would require functional evidence that its modulation can alter melanocyte activity or the hyperpigmented phenotype, together with adequate evidence of specificity, safety, and clinical relevance.

Building on the overview provided by Zhou et al. (2021), the present review specifically examines the

relevance of epigenetic mechanisms to melasma. It brings together evidence on DNA methylation, histone modifications, and ncRNAs, while distinguishing findings from melasma studies from those obtained in experimental models of melanogenesis. By critically discussing these findings and highlighting the limitations of current evidence, this review identifies knowledge gaps and directions for future research on the epigenetic regulation of melasma.

This narrative review was based on a literature search conducted in PubMed, Scopus, and Web of Science, covering publications available up to 2026. The search focused on studies addressing melasma, melanogenesis, and epigenetic regulation, including DNA methylation, histone modifications, and ncRNAs. Publications were selected according to their relevance to the molecular mechanisms underlying melanogenesis and their potential implications for melasma, prioritizing original mechanistic studies and relevant reviews. Particular attention was given to distinguishing findings obtained directly from melasma studies from those derived from experimental models of melanogenesis.

Given this context, this review aims to analyze and discuss the evidence available in the literature regarding the epigenetic mechanisms involved in regulating melanocyte activity in melasma, with an emphasis on DNA modifications, histone alterations, and the role of ncRNAs, as well as their impact on the expression of genes associated with melanogenesis and the maintenance of the hyperpigmented phenotype.

Molecular architecture of melanogenesis

Melanin is a biopolymer responsible for determining skin, hair, and eye color, in addition to acting as an important natural photoprotector. This pigment is biosynthesized through a biochemical pathway termed melanogenesis, a process that occurs within melanocytes – cells located in the basal layer of the epidermis – and whose product is stored in specialized organelles derived from the endosomal system called melanosomes.[24]

Melanin biosynthetic pathway

Melanogenesis consists of an enzymatic pathway in which proteins of the tyrosinase family, especially tyrosinase, a transmembrane glycoprotein considered the rate-limiting enzyme of this metabolic pathway, catalyze the conversion of the amino acid tyrosine (TYR) into either eumelanin (dark brown) or pheomelanin (yellow-red). This process occurs through the direct or indirect oxidation of TYR into dopaquinone,[24-26] as illustrated in figure 1.

Dopachrome tautomerase (DCT), which also belongs to the tyrosinase family, catalyzes the conversion of dopachrome into 5,6-dihydroxyindole-2-carboxylic acid (DHICA).[27] Tyrosinase-related protein 1 (TYRP1), in turn, catalyzes the oxidation of DHICA, contributing to the formation of eumelanin.[28] Alternatively, in the absence of DCT, dopachrome can undergo spontaneous decarboxylation, giving rise to 5,6-dihydroxyindole, which subsequently polymerizes to form melanin.[29] In the presence of cysteine, dopaquinone can react with cysteine to form cysteinyldopa derivatives, which subsequently undergo cyclization and oxidative polymerization, leading to the formation of pheomelanin.[24]

Regulation of melanogenesis

Melanogenesis initiates with the activation of the cyclic adenosine monophosphate (cAMP)/cAMP response element-binding protein (CREB) signaling pathway through paracrine or autocrine cellular signaling. α-melanocyte-stimulating hormone (α-MSH) constitutes the primary ligand for the melanocortin 1 receptor (MC1R), a G-protein-coupled receptor. Following MC1R activation, an intracellular increase in cAMP levels occurs, which activates CREB and promotes the upregulation of microphthalmia-associated transcription factor (*MITF*) gene expression.

In addition, extrinsic factors such as solar radiation, pollution, drugs, and diet, as well as intrinsic factors including hormones, inflammatory mediators, and biological aging,[30] and paracrine factors such as endothelin-1 and stem cell factor (SCF),[31] promote the activation of distinct intracellular signaling cascades related to the control of melanogenesis. Among these pathways, cAMP/protein kinase A (PKA), mitogen-activated protein kinase (MAPK), Wnt/β-catenin, phosphatidylinositol 3-kinase (PI3K)/Akt, and SCF/c-Kit stand out.[32-34]

Vascular endothelial cells may also contribute to the regulation of melanocyte activity through inflammatory mediators. Interleukin-6, which can be secreted by dermal endothelial cells, has been shown to modulate melanogenesis, whereas other inflammatory mediators may exert either pro- or anti-melanogenic effects depending on the signaling context.[34] In melasma, this endothelial contribution may be relevant given the vascular alterations observed in lesional skin.[6]

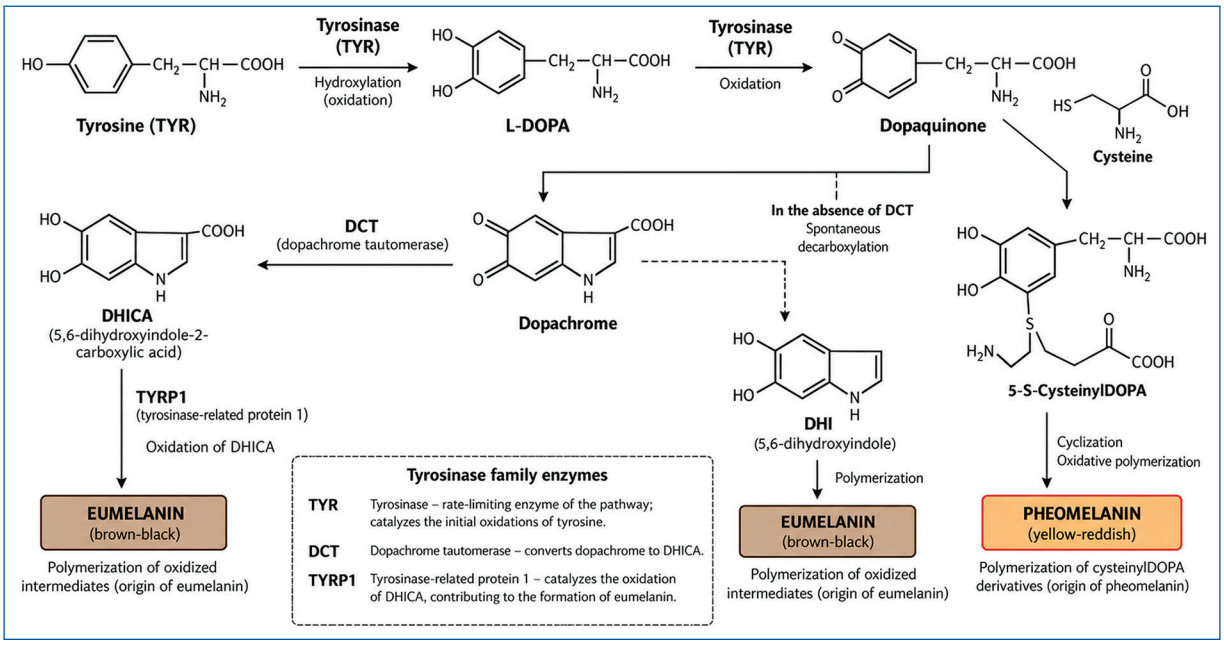

Figure 1. Melanin biosynthetic pathway in melanocytes. Melanogenesis consists of an enzymatic pathway initiated by the oxidation of tyrosine into DOPA and, subsequently, into dopaquinone, which is catalyzed by tyrosinase, the rate-limiting enzyme of the process. From dopaquinone, intermediates such as dopachrome are formed, which can be converted into 5,6-dihydroxyindole-2-carboxylic acid through the action of dopachrome tautomerase (DCT), followed by oxidation mediated by tyrosinase-related protein 1, culminating in the formation of eumelanin. Alternatively, in the absence of DCT, dopachrome can undergo spontaneous decarboxylation, giving rise to 5,6-dihydroxyindole, which polymerizes to form melanin.

Transcription factors involved

MITF, a common target of multiple signal transduction pathways, acts as a master transcription factor that coordinates gene programs by activating the expression of key genes involved in melanogenesis, such as TYR, TYRP1, and DCT, in addition to the structural matrix protein of the melanosome (PMEL). Transcription factor families such as Pax3 and Sox also participate in regulating *MITF* gene expression.[35] Thus, MITF plays a fundamental role in the differentiation, survival, and maintenance of the melanocyte phenotype.[24,36,37]

There is also a synergistic functional relationship between melanocytes and keratinocytes, termed the epidermal melanin unit, which consists of a single melanocyte connected to approximately 10-36 adjacent keratinocytes through dendritic processes.[24,38]

Melanosome biogenesis and maturation

The process of melanogenesis also involves complex stages of maturation and transport of melanogenic proteins. Initially, tyrosinase undergoes glycosylation in the endoplasmic reticulum, a process regulated by proteins responsible for maintaining cellular protein homeostasis through folding and quality-control mechanisms, termed chaperones, among which calnexin stands out prominently.[39,40] The addition of oligosaccharide chains is essential for the structural stability and enzymatic activity of tyrosinase.

Following proper folding in the endoplasmic reticulum, tyrosinase is transported to the Golgi complex, where it undergoes additional modifications and is subsequently targeted, through vesicles originating from the trans-Golgi network, to the melanosomes. Molecules and regulatory cofactors of melanogenesis derived from keratinocytes can also be internalized and participate in vesicular transport processes.[24,41] This transport is regulated by GTP-binding proteins, adaptor proteins, and PI3K.[39-46]

In the early stages of maturation, structural proteins such as PMEL (Pmel17), stabilized by melan-A (MLANA/MART-1), organize an intraluminal fibrillar matrix that serves as a scaffold for the orderly deposition of pigment – a fundamental step for early melanogenesis and proper melanosome morphogenesis.[47]

As pigment synthesis progresses, the melanosome acquires a distinct internal structural arrangement depending on the type of melanin produced. Melanosomes predominantly producing eumelanin display an elongated shape and an organized fibrillar matrix, whereas those producing pheomelanin tend to exhibit a more rounded morphology and a granular internal organization.

Upon complete melanization (stage IV), mature melanosomes are transported along the dendritic processes of the melanocyte through a molecular complex composed of Rab27a, melanophilin (MLPH), and myosin Va (MYO5A). Within this complex, MLPH establishes a direct link between Rab27a and myosin Va, thereby tethering the melanosome to the actin-dependent motor system.[48] This mechanism enables the peripheral displacement of the organelle and the subsequent transfer of pigment to epidermal keratinocytes.[26] Figure 2 summarizes the main stages of this process.

In this manner, melanogenesis is regulated by a complex network of signaling pathways and transcription factors. The activity of these regulators can be modulated not only by environmental and hormonal stimuli but also by epigenetic mechanisms capable of altering chromatin accessibility and melanocytic gene expression. In this context, epigenetic modifications emerge as potential modulators of melanogenic activity and may contribute to the maintenance of the hyperpigmented phenotype observed in melasma.

Epigenetics in melasma

The term “epigenetic landscape,” proposed by the British geneticist Conrad Hal Waddington in 1939 and subsequently used to describe the molecular processes that allow the manifestation of a specific phenotype from the same genotype, constituted the initial milestone for the development of the concept of epigenetics.[14]

Objections to a strictly genetic interpretation of the phenotype emerged from observations in monozygotic twins, who, despite sharing identical genetic material, frequently present discordance regarding the development of certain diseases – that is, one individual being affected while the other is not. Based on this evidence, the understanding was consolidated that the DNA sequence alone does not determine the complexity of the phenotype in its entirety.[49-51]

Gene expression is regulated by mechanisms capable of activating or repressing specific genes, thereby modulating cellular pathways directly related to tissue homeostasis and pathological processes.[19] In this context, epigenetics establishes itself as the scientific field dedicated to studying chemical modifications of the genome and alterations in gene expression that do not involve changes in the underlying DNA sequence.[14,15]

Such modifications influence DNA accessibility to the transcriptional machinery, meaning that the chromatin state can be inherited or acquired, both of which are potentially reversible.[13] Among the primary epigenetic mechanisms, DNA methylation stands out, involving the addition of a methyl group (–CH3) to cytosine residues within CpG islands, which is generally associated with transcriptional repression.[13]

The repression of transcriptional activity can occur either through the physical hindrance of transcription factor binding to DNA or through the recruitment of repressor proteins, such as MeCP2 and MBD1. These repressors, in turn, recruit protein complexes, including histone deacetylases and chromatin remodelers, thereby promoting greater compaction and the subsequent inaccessibility of the chromatin.[52]

The conversion of cytosine to 5-methylcytosine (5 mC) occurs after DNA replication and is catalyzed by DNMTs, such as DNMT1, DNMT3a, and DNMT3b.[13] DNMT1, which is predominantly expressed in the hair follicle and the basal layer of the epidermis, is responsible for maintaining methylation patterns following cell division by copying the pattern from the parent strand to the daughter strand. Furthermore, this enzyme contributes to genomic stability by maintaining epigenetic patterns associated with chromatin integrity and by interacting with proteins involved in the DNA damage response. The relevance of this process is evidenced by its association with embryonic inviability and early lethality in models deficient in methylation maintenance.[53,54]

Within the basal layer of the epidermis, DNMT3a and DNMT3b are also expressed and are responsible for *de novo* methylation in previously unmethylated regions during cellular differentiation processes.[55-58] Although these enzymes are believed to participate in the methylation of non-epidermal genes in undifferentiated skin cells, their specific role in tissue homeostasis remains to be fully elucidated.[13]

It is estimated that approximately 80% of CpG sequences are methylated in mammals, whereas the remaining 20% are predominantly concentrated within CpG islands located in promoter regions. In pluripotent cells, 5 mC has also been identified at CpA and CpT sites.[59] Although classically associated with transcriptional repression, DNA methylation can also, in certain

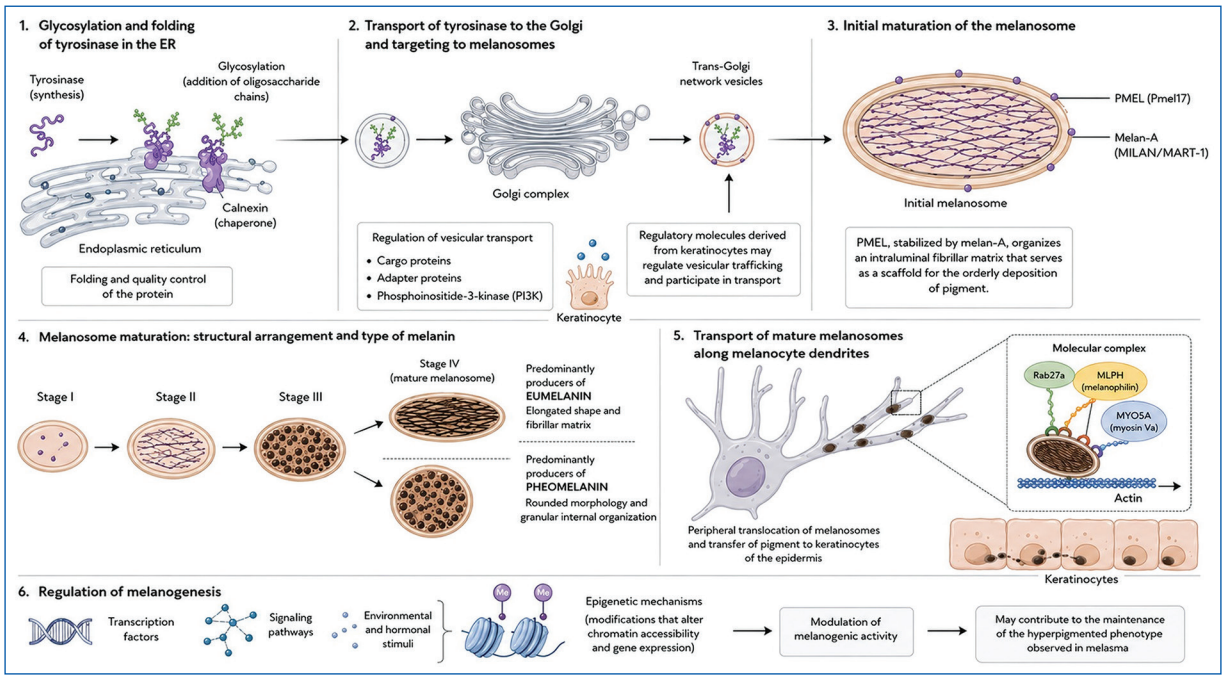

Figure 2. Maturation, transport, and regulation of the melanogenic machinery in melanocytes. Representative schematic showing the stages of tyrosinase glycosylation, maturation, and trafficking; melanosome formation and structural organization; dendritic transport mediated by the Rab27a-MLPH-MYO5A complex; and the regulation of melanogenesis by signaling pathways, transcription factors, and epigenetic mechanisms.

contexts, favor gene activation through the recruitment of specific proteins, such as C/EBPα.[60,61]

DNA methylation and regulation of melanogenesis in melasma

DNA methylation represents a potential mechanism involved in the regulation of melanogenesis and may contribute to the molecular processes associated with melasma.[62] This epigenetic mechanism can influence gene expression and, potentially, the paracrine signaling interactions among keratinocytes, fibroblasts, and melanocytes within the epidermal–dermal unit. However, direct evidence establishing its contribution to melasma pathogenesis remains limited.

Evidence from other biological models supports the involvement of DNA methylation in pigmentation regulation. In a comparative study of crucian carp (*Carassius carassius*), differences in DNA methylation profiles were identified between skin color variants, involving genes associated with melanogenesis, including mitfa, tyr, dct, foxd3, and hpda. Differentially methylated sites were also associated with signaling pathways involved in pigmentation, such as MAPK, cAMP, and Wnt. Although these findings demonstrate an association between DNA methylation and pigmentation-related gene expression, their applicability to human melanogenic disorders, including melasma, remains uncertain.[63]

In human skin-related models, epigenetic regulation of the Wnt pathway has also been investigated. Yamada et al. demonstrated that ultraviolet B (UVB) irradiation induced hypomethylation of the *WNT1* promoter and increased its expression in immortalized human interfollicular epidermal stem cells. Furthermore, reduced DNMT1 expression and decreased methylation of the *WNT1* promoter were observed in solar lentigines compared with non-lesional skin. These findings suggest that UV-induced epigenetic alterations may contribute to pigmentation-related processes in human skin. Nevertheless, whether similar mechanisms operate in melasma has not been directly established.[64]

Environmental factors, particularly UVR, are also associated with changes in cutaneous DNA methylation patterns. A comparative analysis of human skin samples revealed widespread genomic hypomethylation associated with aging and chronic sun exposure, highlighting the influence of environmental and age-related factors on the skin epigenome. Although these findings were not obtained from melasma lesions,

they provide relevant insights into the epigenetic consequences of chronic environmental exposure in human skin.[65,66]

Consistent with these observations, UVB irradiation has been associated with alterations in DNA methylation-related pathways in epidermal cells. In HaCaT keratinocytes, increased expression of TET proteins and elevated 5-hydroxymethylcytosine (5 hmC) levels were reported following UVB exposure, suggesting a potential involvement of active DNA demethylation-related processes in the cellular response to UVR. However, these findings do not establish a direct relationship with melasma or demonstrate corresponding changes in global 5 mC levels.[67]

Collectively, these studies support the potential involvement of DNA methylation in the regulation of pigmentation and cutaneous responses to environmental stimuli. However, most available evidence derives from non-melasma models, emphasizing the need for studies directly investigating DNA methylation patterns in lesional and non-lesional skin from individuals with melasma.

Histone modifications and epigenetic control of melanogenesis

Post-translational modifications of histones constitute one of the primary epigenetic mechanisms involved in the regulation of gene expression, operating through the modulation of chromatin structure and DNA accessibility to the transcriptional machinery.[13] Chromatin is dynamic and highly regulated, organized into fundamental units called nucleosomes, which are composed of a histone octamer – formed by two H2A-H2B dimers and one H3-H4 tetramer – around which approximately 147 DNA base pairs are wound.[68]

Modifications to the N-terminal tails of histones occur predominantly at amino acid residues such as lysines and arginines and include processes such as acetylation, methylation, phosphorylation, and ubiquitination. These modifications can act in an activating or repressing manner on gene transcription depending on the specific residue modified, the degree of modification, and the structural context of the chromatin; therefore, they do not configure a strictly linear or canonical regulatory system.[13,69,70]

In general, modifications associated with transcriptional activation promote chromatin relaxation (euchromatin), favoring the access of transcription factors and enzymatic complexes to the DNA. Conversely, repressive modifications contribute to chromatin compaction (heterochromatin), restricting gene accessibility and promoting transcriptional silencing.

Among the most extensively studied epigenetic marks, modifications of histone H3 stand out prominently. The H3K4me2/3 and H3K36me2/3 marks are associated with gene activation, whereas H3K9me2/3 and H3K27me2/3 are related to transcriptional silencing. In highly compacted genomic regions, such as telomeres and centromeres, a predominance of H3K9me is observed, which is associated with heterochromatin formation and the maintenance of genomic stability, including processes such as X-chromosome inactivation.[69] Conversely, the H3K27 modification plays a more dynamic regulatory role, acting as a transient marker in gene regulatory regions during cellular differentiation processes.[71]

In this context, histone modifications play a central role in regulating fundamental cellular processes, including proliferation, differentiation, and the response to environmental stimuli. Alterations in these mechanisms – whether due to the dysfunction of modifying enzymes or changes in the pattern of epigenetic marking – can contribute to the development and maintenance of pathological conditions, including pigmentary disorders.

Histone acetylation and activation of melanogenesis

In the context of melanogenesis, histone acetylation represents the epigenetic modification most frequently associated with the transcriptional activation of melanogenic genes.[62] Acetylation of lysine 27 on histone H3 (H3K27ac) is widely observed in melanocyte enhancer regions and is directly related to the activation of gene programs specific to this cellular phenotype.[72]

From a molecular standpoint, DNA carries a negative charge, whereas histones possess a positive charge, which favors electrostatic interaction between these structures and contributes to chromatin compaction. The action of histone acetyltransferases, by adding acetyl groups (-$COCH_3$) to the protonated amino groups (-NH_3^+) of lysines, promotes the partial neutralization of this positive charge, resulting in chromatin relaxation and increased DNA accessibility to the transcriptional machinery.

This process is, in part, mediated by the transcription factor MITF, considered the central regulator of melanogenesis, which operates by recruiting transcriptional coactivators, such as p300 and CREB-binding protein (CBP), to the promoter regions of target genes. This

recruitment favors histone acetylation and the subsequent activation of melanogenic gene transcription, including TYR, TYRP1, and DCT.[62]

In addition, MITF contributes to the modulation of the intracellular microenvironment by regulating the expression of carbonic anhydrase 14, thereby promoting local alkalization, which can potentiate the activity of the CBP/p300 complex and amplify the active transcriptional state.

The activation of this epigenetic axis is intimately related to extracellular stimuli, particularly UVR. Exposure to UVR induces keratinocytes to secrete α-MSH, which binds to the MC1R receptor on melanocytes, promoting adenylate cyclase activation and an increase in intracellular cAMP levels. This increase leads to the activation of PKA, which phosphorylates the transcription factor CREB, culminating in the recruitment of CBP/p300 and the activation of the epigenetic machinery associated with histone acetylation.[73]

Thus, histone acetylation acts predominantly in the maintenance and amplification of the melanogenic program, consolidating an active transcriptional state previously established by intracellular signaling pathways, such as the cAMP/CREB axis. Nonetheless, despite recent advances, the epigenetic mechanisms involving histone modifications in melanogenesis – especially in the context of melasma – still require further experimental elucidation.

ncRNAs and epigenetic regulation of melanogenesis

The human genome behaves as a complex system of control, regulation, and construction. In this context, only approximately 2% of the human genome consists of protein-coding sequences, whereas a large proportion of the remaining genomic sequence is non-protein-coding and contributes to diverse regulatory processes. ncRNAs, transcribed from non-protein-coding regions of the genome, represent important components of these regulatory mechanisms.[74]

The ncRNAs can be classified into different categories according to their size and structural conformation, including miRNAs, long ncRNAs (lncRNAs), and circular RNAs (circRNAs), all of which play relevant roles in the regulation of melanogenesis.

miRNAs

miRNAs are small ncRNAs of approximately 20-22 nucleotides that regulate gene expression post-transcriptionally.[75] They display partial complementarity with one or multiple messenger RNAs and do not encode proteins, thereby contributing to the regulation of gene expression through mechanisms such as translational repression, transcript destabilization, and deadenylation.[19,75,76]

miRNAs play a relevant role in a variety of cellular processes, including division, development, and differentiation. Furthermore, alterations in their expression are associated with pathological conditions, such as pigmentary disorders.[77,78] Consequently, they have been extensively investigated as potential biological markers and ancillary tools in clinical diagnosis.

In this scenario, considering the interdependence among epigenetic regulation, cellular differentiation, and the response to the tissue microenvironment, it is fundamental to understand how these mechanisms integrate into melanogenesis.

miRNAs play a critical role in regulating melanogenesis, operating at different levels of the process, ranging from the direct modulation of melanogenic enzymes to interference with signaling pathways and transcription factors. According to the literature, these miRNAs can be classified based on their origin and molecular targets, allowing for a better understanding of their mechanisms of action.[62] Based on this classification, table 1 presents the organization of the primary miRNAs involved in melanogenesis.

lncRNAs

lncRNAs are ncRNAs molecules longer than 200 nucleotides that regulate gene expression through the modulation of chromatin, transcription, and post-transcriptional processes, frequently through interactions with DNA, RNA, and proteins. These RNAs also play a relevant role in the regulation of melanogenesis, operating through distinct molecular mechanisms, including the modulation of transcription factors, signaling pathways, and interactions with miRNAs. Evidence demonstrates that several lncRNAs are involved in this process, exerting both positive and negative effects on melanin production.[62] Based on these mechanisms, table 2 presents a synthesis of the primary lncRNAs related to melanogenesis and their respective modes of action.

Among the lncRNAs investigated in the context of melasma, H19 has received particular attention. Reduced H19 expression has been reported in hyperpigmented skin from individuals with melasma. In experimental models, H19 silencing in keratinocytes

Table 1. Classification of miRNAs involved in melanogenesis according to their origin and mechanism of action

Group	Origin of miRNAs	Molecular target	Main miRNAs	Mechanism of action/biological effect
1	Melanocytes	Melanogenic protein genes	miR-125b, miR-155, miR-143-5p, miR-145, miR-203, miR-510, miR-1291	Direct regulation of melanin synthesis, melanogenic enzymes, or melanosome transport
2	Melanocytes	Transcription factors (mainly MITF and SOX family)	miR-141a-3p, miR-200a-3p, miR-340, miR-218, miR-25, miR-183, miR-148a, miR-508-3p, miR-137, miR-145, miR-21a-5p, miR-155, miR-380-3p	Inhibition of MITF expression and negative regulation of pigmentation-related genes; indirect modulation through the SOX family
3	Melanocytes	Signaling pathways	miR-21, miR-206, miR-137, miR-379, miR-27a-3p, miR-125b	Inhibition of pathways such as α-MSH/MC1R, SCF/c-Kit, MAPK/ERK, Wnt, and mTOR
4	Keratinocytes	Paracrine factors	miR-488, miR-7	Reduction of POMC production and, consequently, ACTH, β-endorphin, and α-MSH; inhibition of FGF2 and indirect modulation of the MAPK pathway in melanocytes
5	Keratinocytes (through exosomes)	Melanocytes (intercellular communication)	Not specified	Transfer of miRNAs through exosomes, modulating melanocytic function

Source: Author's synthesis based on the original studies cited in the table and Zhou et al. (2021).
MITF: microphthalmia-associated transcription factor; miRNAs: microRNAs; α-MSH: α-melanocyte-stimulating hormone; SCF: stem cell factor; MAPK: mitogen-activated protein kinase.

Table 2. Main lncRNAs involved in melanogenesis and their mechanisms of action

lncRNA	Molecular target/pathway	Mechanism of action	Effect on melanogenesis
H19	miR-675/MITF; p53/α-MSH	miR-675 derived from H19 inhibits MITF; reduction of H19 activates p53 and increases α-MSH secretion	Dual regulation (MITF inhibition; indirect stimulation through α-MSH)
TUG1	ERK pathway	Inhibits the ERK signaling pathway	Negative regulation
UCA1	CREB/MITF axis; cAMP/PKA, ERK, and JNK pathways	Inhibits multiple signaling pathways associated with melanogenesis	Negative regulation
lnc-TCONS_00049140	Not specified	Not detailed in the cited literature	Not specified
ENST00000606533	Not specified	Not detailed in the cited literature	Not specified
SRA	Not specified	Not detailed in the cited literature	Not specified

Source: Author's synthesis based on Kim et al. (2010; 2014) and Zhou et al. (2021).
lncRNA: long ncRNAs; CREB: cAMP response element-binding protein; α-MSH: α-melanocyte-stimulating hormone; PKA: protein kinase A; MITF: microphthalmia-associated transcription factor.

was associated with increased tyrosinase expression and melanosome transfer in keratinocyte-melanocyte cocultures, whereas no comparable effect was observed in melanocyte monocultures. These findings suggest that H19 may influence melanogenesis through intercellular interactions rather than solely through cell-autonomous mechanisms.[79]

Further investigations have explored the role of miR-675, a miRNA derived from H19, in the regulation of melanogenesis. Its release by keratinocytes through exosomes and its interaction with MITF have been described, with experimental evidence indicating that miR-675 can directly target MITF. Increased miR-675 expression was associated with reduced MITF levels

and downregulation of melanogenic genes, whereas its inhibition produced opposite effects. Collectively, these findings suggest a potential H19/miR-675/MITF regulatory axis connecting keratinocyte–melanocyte communication to melanogenesis. However, the available mechanistic evidence is largely derived from experimental models, and the contribution of this axis to melasma pathogenesis remains to be further elucidated.[80]

circRNAs

The circRNAs constitute a class of ncRNAs characterized by a loop structure resulting from the covalent linkage between the 3' and 5' ends. This conformation confers greater stability compared to linear RNAs and enables a broad functional diversity. These RNAs operate principally as miRNA "sponges," thereby modulating gene expression, and can additionally serve as templates for protein translation as well as participate in the regulation of paracrine axes between different cell types.[62,81]

In the literature, approximately 5,396 circRNAs have been identified in human melanocytes,[82] highlighting their biological relevance. In this context, it is observed that circRNAs also participate in the regulation of melanogenesis, given that their expression can be modulated by external stimuli, such as exposure to α-MSH, directly influencing melanin production.[62] Based on these findings, table 3 presents the primary circRNAs involved in melanogenesis and their respective mechanisms of action.

Based on the accumulated evidence, ncRNAs exert a central role in the epigenetic regulation of melanogenesis, operating in an integrated manner across different levels of gene control. miRNAs, lncRNAs, and circRNAs modulate the expression of genes, transcription factors, and signaling pathways, directly influencing melanocyte activity and melanin production. These mechanisms reinforce the complexity of epigenetic regulation in melasma and underscore the potential of ncRNAs as promising therapeutic targets and biomarkers, although further studies remain necessary to fully elucidate their interactions and clinical applications.

Skin aging and oxidative stress in the regulation of melanogenesis

Oxidative stress and melanogenesis

Reactive oxygen species (ROS), generated primarily as a byproduct of mitochondrial oxidative phosphorylation, play a relevant role in the regulation of melanogenesis, given that they actively participate in cell signaling processes and the modulation of gene expression. These molecules, such as the superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical (•OH), exhibit high chemical reactivity and the capacity to interact with biomolecules, directly influencing cellular function.[83-85]

At physiological levels, ROS act as secondary messengers in distinct intracellular signaling pathways, contributing to the regulation of processes such as cellular proliferation, angiogenesis, and tissue repair.[86-89] Thus, both an excess and a deficiency of ROS can compromise cellular homeostasis, and excessively low levels can even interfere with cell cycle progression.[90,91] However, the maintenance of redox homeostasis is essential, since an imbalance in this system can alter the activation pattern of signaling pathways previously described in melanogenesis, including the cAMP/CREB/MITF axis, which is central to the regulation of melanocyte activity.

Within the context of the epidermal melanocytic unit, oxidative stress also interferes with paracrine communication among keratinocytes, fibroblasts, and melanocytes, modulating the release of mediators that influence melanogenic activity. In this scenario, the activation of the p53 protein in keratinocytes, induced by oxidative damage and UVR, promotes the transcription of POMC, resulting in increased production of α-MSH and the subsequent activation of the MC1R receptor on melanocytes. This mechanism integrates environmental signals into the regulation of melanogenesis, converging on the activation of MITF, as previously discussed.[85]

Beyond the direct modulation of signaling pathways, oxidative stress can influence the epigenetic regulation of gene expression. Alterations in the cellular redox state can interfere with the activity of enzymes involved in DNA methylation and histone modifications, impacting chromatin accessibility and, consequently, the expression of genes related to melanogenesis.[85] Thus, oxidative stress can act as an indirect modulator of melanocyte activity, reinforcing or sustaining previously established transcriptional patterns.

Although ROS are predominantly generated within the mitochondria and the endoplasmic reticulum, other intracellular sources also contribute to their production, including the NADPH oxidase (NOX) family, the uncoupling of nitric oxide (NO) synthase, peroxisomes, and melanosomes. Considering that the melanogenesis process itself occurs within an intrinsically oxidative

Table 3. Main circRNAs involved in melanogenesis and their mechanisms of action

circRNA	Molecular target/pathway	Mechanism of action	Effect on melanogenesis
circ_0091223	miR-1291/tyrosinase (TYR)	Acts as a "sponge" for miR-1291, reducing its inhibitory effect on TYR	Positive regulation (promotion of melanogenesis)
CiRS-7	miR-7/FGF2 (paracrine axis)	Regulates the miR-7/FGF2 axis in keratinocytes and fibroblasts, with paracrine modulation on melanocytes; expression increased by UVB radiation	Positive regulation (induction of melanogenesis)

Source: Author's synthesis based on the original studies cited in the table and Zhou et al. (2021).[62]
circRNAs: circular RNAs; UVB: ultraviolet B; FGF2: fibroblast growth factor 2.

environment, an increase in these species can amplify the local pro-oxidant state, favoring functional alterations in the involved cells.[85]

Corroborating these aspects, patients with melasma exhibit elevated serum levels of oxidative stress markers, such as superoxide dismutase, glutathione peroxidase, and malondialdehyde.[92,93] However, these findings suggest not merely a global increase in ROS, but a selective redox imbalance in which different reactive species and antioxidant systems display distinct behaviors.[94,95] An increase in NO, for instance, can contribute to nitrosative stress, favoring peroxynitrite formation and intensifying molecular damage.[92] This scenario reinforces the presence of a cutaneous microenvironment characterized by chronic low-grade inflammation, wherein oxidative stress, cell signaling, and epigenetic mechanisms operate in an integrated manner to maintain the hyperpigmented phenotype of melasma (Fig. 3).

Skin aging and epigenetic alterations

The skin is constantly subjected to cellular renewal processes throughout life, which are dependent on stem cell activity and the maintenance of tissue homeostasis. With aging, a progressive decline in this regenerative potential is observed, accompanied by the accumulation of macromolecular damage and reduced efficiency of cellular repair mechanisms.[96,97]

Among the alterations associated with skin aging, epigenetic modifications and the onset of cellular senescence stand out, characterized by cell cycle arrest, chromatin reorganization, and changes in the secretory profile. These processes reflect shifts in the regulation of gene expression, including alterations in DNA methylation patterns and histone modifications, as previously discussed.[96,98]

In the context of melasma, these alterations assume a relevant role, given that lesions are frequently associated with photoaged areas that exhibit dermal matrix impairment, increased vascularization, and alterations in the interaction among cells within the epidermal-dermal unit. This environment favors the maintenance of an active transcriptional state in genes related to melanogenesis, contributing to the persistence of hyperpigmentation.

In addition, aging is associated with greater genomic instability and a reduced capacity to respond to DNA damage – factors that can potentiate the dysregulation of signaling pathways and epigenetic mechanisms.[99] In this scenario, previously established alterations in gene regulation, including those mediated by DNA methylation, histone modifications, and ncRNAs, can be maintained or amplified, favoring sustained melanocyte activity.

Thus, skin aging acts as a permissive factor that, in association with oxidative stress and exposure to environmental factors, contributes to the maintenance of epigenetic alterations and signaling pathways involved in melanogenesis. These integrated processes sustain the hyperpigmented phenotype observed in melasma.

Conclusion

The analysis of the available scientific evidence demonstrates that the pathogenesis of melasma extends beyond melanocyte hyperactivity and involves a complex regulatory network in which epigenetic mechanisms may interact with environmental, cellular, and microenvironmental factors. DNA methylation, histone modifications, and ncRNAs have been implicated in the regulation of melanogenic pathways and may influence the expression of genes and signaling mechanisms associated with melanocyte activity. However, the current evidence remains insufficient to determine whether these epigenetic alterations represent primary mechanisms contributing to melasma or secondary responses to UVR, oxidative stress, inflammation, and

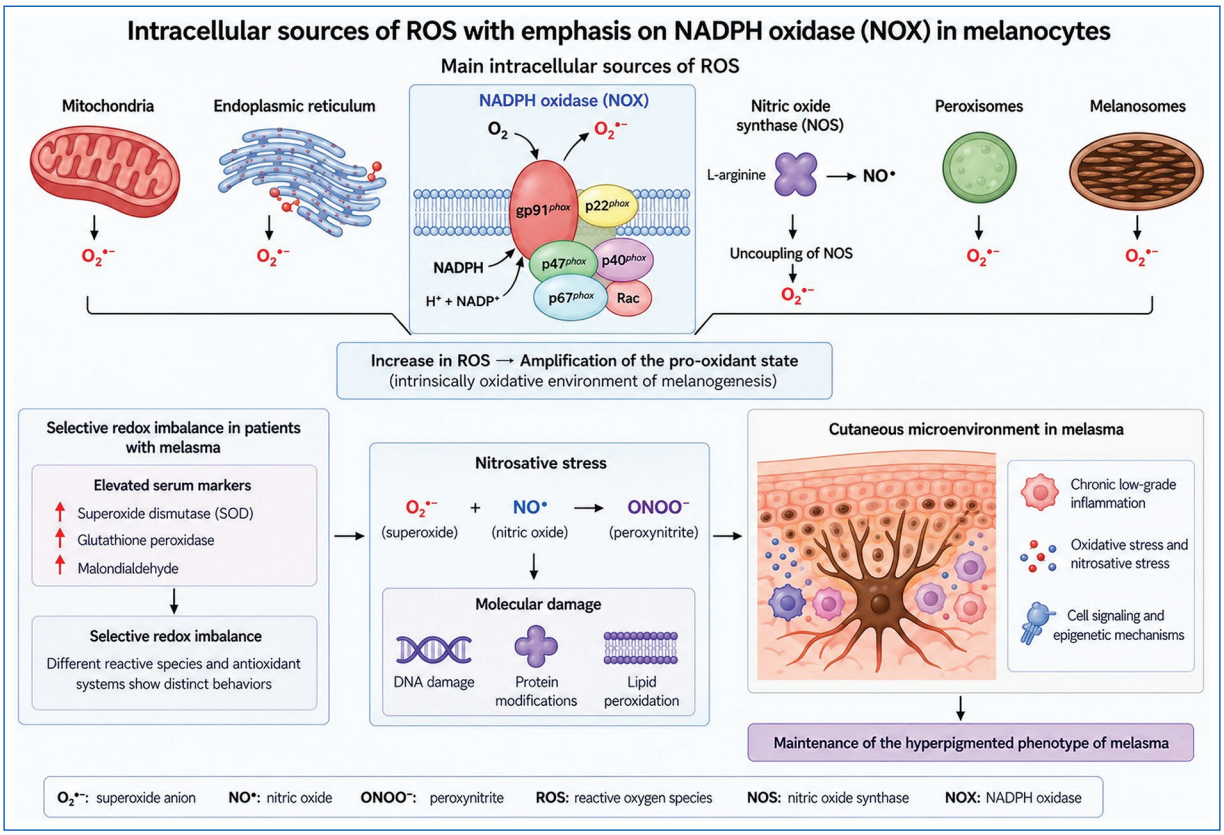

Figure 3. Intracellular sources of reactive oxygen species (ROS) with emphasis on NADPH oxidase (NOX) and its implications in melasma. Schematic representation of the primary intracellular sources of ROS, emphasizing NOX, and their contribution to the intensification of the pro-oxidant state, nitrosative stress, redox imbalance, and maintenance of the inflammatory microenvironment associated with melasma.

other microenvironmental stimuli. In this context, ncRNAs and histone modifications identified in melanogenesis, together with DNA methylation changes reported in melasma, provide relevant avenues for further investigation. Their potential application as biomarkers or therapeutic targets remains promising but requires validation in independent populations, direct comparison of lesional and non-lesional skin, and functional studies establishing their biological and clinical relevance. Overall, melasma should be considered a multifactorial disorder in which epigenetic mechanisms may contribute to the regulation and persistence of melanogenic activity, in interaction with oxidative stress, skin aging, and the cutaneous microenvironment.

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Generative artificial intelligence tools were used exclusively for linguistic revision, text organization, and figure formatting. All scientific content, interpretation, and critical analysis were performed entirely by the authors.

Data availability

No new data were generated or analyzed in this study.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of people and animals. The authors state that, for this research, no experiments were conducted on humans or animals.

Confidentiality, informed consent, and ethical approval. The study does not involve patients' personal data and does not require ethical approval. The SAGER guidelines do not apply.

Statement on the use of artificial intelligence. The authors declare that ChatGPT, Manus, Notebook LM, and other tools were used for text organization, linguistic review, and the production of images and tables in this work. The scientific content, including the selection, analysis, and interpretation of information, was developed entirely by the author, who assumes full responsibility for the originality and academic rigor of the material presented.

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