Melasma pathogenesis: a review of the latest research, pathological findings, and investigational therapies

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Abstract

Melasma is an acquired hyperpigmentation disorder most commonly affecting females with darker skin types. It is triggered by several factors including sun exposure, genetic influences, and female sex hormones. The pathology of melasma extends beyond melanocytes and recent literature points to interactions between keratinocytes, mast cells, gene regulation abnormalities, neovascularization, and disruption of basement membrane. This complex pathogenesis makes melasma difficult to target and likely to recur post treatment. A better understanding of the latest pathological findings is key to developing novel and successful treatment options. This review aims to provide a summary of the more novel pathological findings and latest investigational therapies.

Keywords: melasma, hyperpigmentation, melasma pathogenesis, melasma treatment

Introduction

Melasma is an acquired hyperpigmentation that is characterized by bilateral irregular brown macules and patches on sun exposed areas of the face and less frequently, the forearms [1]. It is most commonly found in darker skinned females — typically Asian or Hispanic women — with Fitzpatrick skin types III-IV. It is triggered by a variety of factors including sun exposure, genetics, and female sex hormones [2]. The pathology of melasma is complex although it was initially thought to involve only melanocytes. Evolving research points to a more heterogeneous pathogenesis involving an interplay of keratinocytes, mast cells, gene regulation abnormalities, increased vascularization, and basement membrane disruption [3]. It is essential that clinicians are familiar with the evolving pathogenesis of melasma, as this may aid in successful combination treatment options for this notoriously difficult and relapsing condition. This review aims to provide a summary of the more novel pathological findings and latest investigational therapies.

Discussion

Publications describing melasma pathogenesis were primarily found through a PubMed literature search. Keywords included: melasma, pathology, melanogenesis, melanocytes, keratinocytes, mast cells, ultraviolet (UV) radiation, basement membrane, vascularization, prostaglandins, estrogen, progesterone, therapeutics, and tranexamic acid. Several articles were reviewed for relevancy from 1981 to 2018 and references of the selected articles were also searched for relevant articles. A total of 35 references were included. Literature included was of a variety of types including basic science research, randomized controlled trials, commentaries, and reviews.

Melanocytes

The increase in the amount of melanin production in melasma is well accepted. However, whether or not this increase is accompanied by a quantitative increase in melanocytes is debated [4, 5]. The specific mechanisms behind increased melanin deposition are still being elucidated. It has been shown that UV

radiation leads to an upregulation of melanocyte-stimulating hormone (MSH) receptors — also known as melanocortin-1 receptors (MC1-R) — on melanocytes, allowing for greater binding of the hormones and therefore more melanin production [6]. Proopiomelanocortin (POMC) is cleaved to produce the peptides α-melanocyte stimulating hormone (α-MSH) and adrenocorticotropic hormone (ACTH) in response to UV [7]. When these peptides bind to and activate MC1-R, they increase levels of protein kinase A (PKA), which phosphorylates the cAMP response element (CREB), (**Figure 1**).

cAMP response element is a transcription factor for microphthalmia associated transcription factor (MITF), a key regulator in the melanin synthesis pathway. Microphthalmia associated transcription factor controls the expression of tyrosinase, an enzyme responsible for several steps in melanogenesis [8]. UV radiation is also shown to endogenously generate 1,2-diacylglycerols (DAGs), a type of second messenger, from plasma membrane phospholipids of melanocytes via phospholipase C and D (PLC and PLD) pathways. These DAGs go on to activate tyrosine and therefore increase melanogenesis (**Figure 1**), [9].

The tumor suppressor protein p53 may also play a role in UV-induced melanogenesis. This protein upregulates POMC production in keratinocytes post UVB damage, which leads to increased melanin production. In addition, the protein also increases transcription of hepatocyte nuclear transcription factor-1alpha (HNF-1alpha), which induces tyrosinase downstream to increase melanin

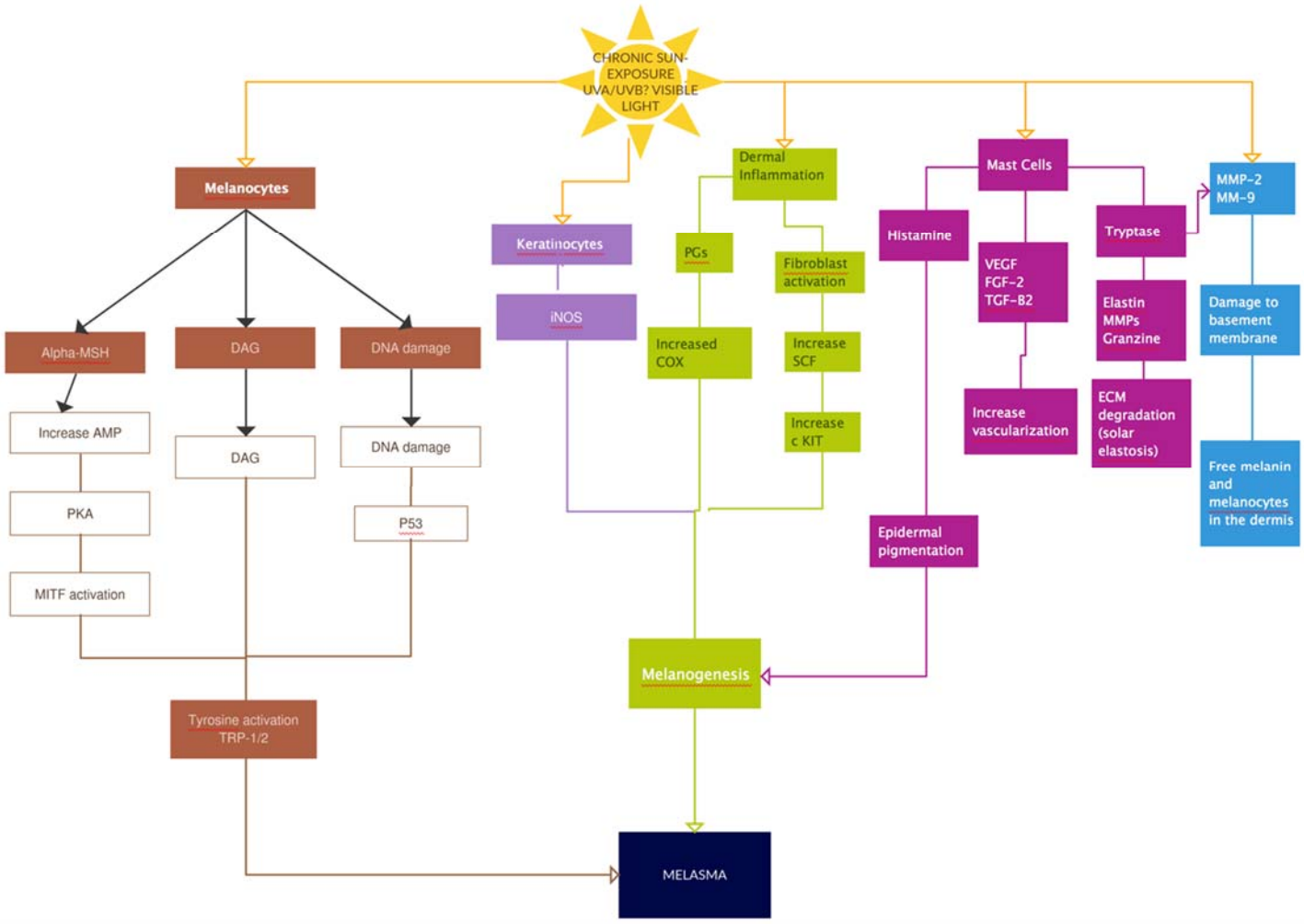

Figure 1. *Flow diagram showing the total number of mobile apps found from the Apple App Store and the number of apps excluded from analysis (including reason for removal).*

production even in the absence of keratinocytes (**Figure 1**), [8]. Although the above pathways induce melanogenesis in all skin, the response to UV light is exaggerated and expression of α-MSH is sustained in melasma lesions, augmenting the production of melanin [7].

Solar Elastosis and Photoaging

Solar elastosis refers to the accumulation of abnormal elastic tissue in the dermis resulting from chronic sun exposure or photoaging. Melasma patients have been found to have high levels of solar elastosis in affected skin. In addition, histological analysis shows that melasma skin tends to have thicker and more curled and fragmented elastic fibers when compared to normal skin [3].

Ultraviolet B exposure can stimulate keratinocytes to increase melanocyte and therefore, melanin production by secreting various growth factors, cytokines, and hormones including inducible nitric oxide synthase or iNOS [10]. UVB irradiation also increases plasmin production by keratinocytes. This enzyme leads to higher levels of arachidonic acid and alpha-MSH and therefore stimulates the melanin synthesis pathway [11]. These factors all lead to hyperpigmentation of the affected skin. Furthermore, it has been suggested that even visible light may play a role in the pathogenesis of melasma, especially in darker skin types (Fitzpatrick types IV-VI), by interacting with the opsin 3 sensor (**Figure 1**), [12].

Mast Cells and Neovascularization

Numbers of mast cells are higher in melasma skin than in unaffected skin [8]. UV exposure triggers the release of histamine from these mast cells, leading to downstream effects [13]. Histamine binding at the H2 receptor activates the tyrosinase pathway and induces melanogenesis. This finding may help elucidate the link between the inflammatory process in UV radiation and the hyperpigmentation that follows [14].

In addition, UV radiation also increases the production of mast cell tryptase, which activates matrix metalloproteinase (MMP) precursors. These active enzymes then go on to degrade type IV collagen and damage the basement membrane. Granzyme B, released directly by mast cells, further damages the extracellular matrix (ECM). Tryptase may also contribute to solar elastosis by triggering the production of elastin [3].

Finally, mast cells induce hypervascularization, another prominent clinical finding in melasma, by secreting proteins such as vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), and transforming growth factor-B (TGF-B). These angiogenic factors increase the size, density, and dilatation of vessels in affected skin, and present another therapeutic target when treating melasma (**Figure 1**), [2, 3].

Basement Membrane Damage

Basement membrane abnormalities play a key role in melasma pathology. As described above, UV damage activates MMP2 and MMP9 to degrade type IV and VI collagen in the basement membrane [3]. Cadherin 11, an adhesion molecule that is upregulated in melasma skin, can then mediate interaction between fibroblasts and melanocytes and promote melanogenesis [15]. Cadherin 11 is also responsible for upregulating MMP1 and MMP2 expression, leading to further collagen degradation and accumulation of elastotic material in melasma skin. These effects may even be independent of UV irradiation [15]. Basement membrane damage also allows the movement of melanocytes and melanin granules down into the dermis, which contributes to the persistent and recurring nature of melasma. Therefore, trauma induced by lasers or any therapies that further aggravate the basement membrane may worsen the disease. Similarly, restoration of the basement membrane may limit recurrence (**Figure 1**), [3].

Dermal Inflammation

Prolonged UV radiation causes dermal inflammation and activates fibroblasts. These cells then secrete stem cell factor (SCF), which may diffuse into and induce melanogenesis in the overlying epidermis [16]. Likewise, levels of stem cell growth factor receptor, also known as c-kit, are also upregulated in melasma lesions. When c-kit binds to SCF, it activates the tyrosine kinase pathway responsible for melanogenesis [17]. Dermal inflammation is also

characterized by increased levels of COX-2 and prostaglandins, further stimulating melanocytes (**Figure 1**), [18].

Hormonal Influence

Estrogen has also been shown to play a role in melasma pathogenesis, which explains its increased prevalence among post-pubertal women, oral contraceptive users, and pregnant women. Studies have shown an increased number of estrogen receptors in the dermis and of progesterone receptors in the epidermis of melasma lesions [19, 20]. Binding of estrogen to its receptors on melanocytes and keratinocytes can activate tyrosinase and MITF pathways to induce melanin production [21]. In addition, increased expression of the PDZ domain protein kidney 1 (PDZK1), which regulates ion exchangers, in melasma lesions could help mediate interactions between estrogen and ion exchangers to increase melanogenesis and melanosome transfer [22]. Estrogen's role presents a unique target for melasma therapy.

Novel Approaches to Therapy

Melasma's complex pathology and recurring nature make it difficult to target therapeutically [1]. Traditionally, melasma has been treated with topical agents, including hydroquinone (which inhibits tyrosinase), tretinoin, corticosteroids, and combination creams with varying formulations (**Table 1**). Hydroquinone has long been the conventional treatment, but the concern over its side effects have prompted the use of potentially safer alternatives. Current therapies include topical agents, chemical peels, laser and light treatments, and systemic agents [23].

Tranexamic acid (TXA), a plasmin inhibitor, has gained popularity as a systemic therapy for melasma and is available in oral, topical, and injectable forms. Plasmin increases arachidonic acid and prostaglandin levels in keratinocytes, leading to increased melanogenesis. Furthermore, plasmin frees ECM-bound VEGF, promoting angiogenesis [24]. Tranexamic acid is therefore one of the few

Table 1. *Melasma pathogenesis and corresponding medical/experimental therapies*

Component	Mechanism of pathogenesis	Therapies	Level of Evidence	Reference
Tyrosine activation	Increases melanogenesis	Hydroquinone Azelaic Acid Glycolic acid siRNA agents Combination creams (*includes retinoid and steroid) Proton-pump inhibitors (*block copper acquisition by tyrosinase, which leads to its degradation)*	2a 1b 2b 2b 1b *Proposed therapy*	Ennes et al. [31] Balina LM and Graupe K [32] Sarkar et al. [33] Xiang Y et al. [27] Nordlund et al. [34] Matsui MS et al. [29]
UVB-induced Keratinocyte stimulation	Increases melanocyte production	Retinoids	1a	Griffiths CE et al. [35]
Neovascularization	Growth-factor induced angiogenesis	Tranexamic acid	1b	Atefi et al. [25]
cAMP accumulation and CREB phosphorylation	Controls downstream melanin synthesis pathways	Metformin	*Proposed therapy*	Lehraiki et al. [28]
Hormonal influence	Binding of estrogen activates downstream melanogenesis pathways	Estrogen antagonist	*Proposed therapy*	Cohen PR [21]

treatments to target the neovascularization present in melasma. A recent double-blinded clinical trial showed topical TXA to be as efficacious as hydroquinone in reducing the mean Melasma Area and Severity Index (MASI) score, with fewer side effects [25]. In another placebo-controlled double-blinded trial, oral TXA was shown to be superior to the placebo for the treatment of moderate-to-severe melasma with minimal side effects [26].

Recent developments in melasma therapy include specific agents targeting various aspects of melasma pathology. Therapeutic alternatives to traditional topicals, such as small interfering ribonucleic acid (siRNA) agents, have been investigated. Microphthalmia associated transcription factor-siRNA administered as a transdermal peptide targets and inhibits the tyrosinase pathway of melanogenesis in a time-dependent manner with no major side effects. This novel option also shows promise in melanoma treatment and is safe enough to use daily [27]. Metformin, an antidiabetic drug which acts by decreasing cAMP levels, has been shown to decrease melanin content in melanocytes by inhibiting downstream synthesis pathways [28]. Proton pump inhibitors (PPIs) such as omeprazole may also inhibit melanogenesis when applied topically. It is hypothesized that PPIs interfere with ATP7A, blocking copper acquisition by tyrosinase, which leads to its degradation and therefore reduces melanogenesis [29]. Most recently, a combination topical therapy has been suggested which combines an estrogen and VEGF antagonist, targeting both melanogenesis and angiogenesis [22].

Laser and light treatments for melasma, including intense pulsed light, target excess pigment in the skin but do not alter the underlying pathology of the disease. As a result, recurrence is common when laser is used as monotherapy. In addition, high intensity lasers can further degrade the basement membrane and allow descent of melanin into the dermis as mentioned above [3].

Regardless of the treatment modality chosen, sun protection is crucial to prevent new lesions and avoid worsening existing melasma [23]. The current recommendation is that patients use a broad-spectrum UVA/UVB sunscreen with at least SPF30 daily, preferably with a physical blocking agent such as zinc oxide or titanium dioxide. Behavioral measures such as wearing wide-brimmed hats or avoiding peak sunlight hours may also help [23]. Recent studies also show that a sunscreen that blocks visible light in addition to UV light may further improve melasma lesions and increase response to traditional lightening agents such as hydroquinone [30].

Conclusion

In conclusion, melasma is a facial hyperpigmentation condition with a varied and evolving pathology. Increased melanogenesis, extracellular matrix alterations, inflammation, and angiogenesis all play a role in the development of melasma. The multifactorial nature of the disease makes it difficult to treat and likely to recur. A better understanding of the pathology is key to developing novel and specific therapeutic options.

Potential conflicts of interest

The authors declare no conflicts of interests.

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