The Role of *MC1R* in UVB-Induced Hyaluronan Dysregulation, and Skin Hydration

A Literature Review

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ABSTRACT

Background. Skin hydration is a central determinant of cutaneous appearance and function, and its deterioration is a prominent feature of age-associated decline in skin quality. Among extrinsic factors, ultraviolet B (UVB) radiation is particularly relevant because it promotes molecular damage within the skin and disrupts hyaluronic acid (hyaluronan, HA) homeostasis, thereby compromising water retention, viscoelasticity, and tissue turgor. Within this context, variation in the melanocortin 1 receptor gene (*MC1R*) may be relevant to hydration biology not through direct regulation of water balance, but through modulation of susceptibility to UV-induced injury. This hypothesis is biologically plausible because *MC1R* is a key regulator of melanocyte responses to UV exposure, including pigmentation, oxidative stress defense, and DNA repair, whereas UVB irradiation is known to disturb cutaneous HA metabolism (Farage et al., 2008; Rouzaud et al., 2005).

Methods. A narrative review was undertaken to synthesize evidence on *MC1R*-associated photobiology, UVB-induced skin damage, and hyaluronan-dependent mechanisms relevant to cutaneous hydration and visible skin quality. Particular emphasis was placed on experimental and clinical studies examining *MC1R*-mediated regulation of melanocyte signaling, pigmentation, oxidative stress responses, and DNA repair, together with investigations addressing UVB-induced alterations in cutaneous hyaluronan metabolism and the effects of preventive or supportive interventions on hydration-related manifestations of skin aging. Preference was given to studies that clarified underlying biological pathways and enabled integration of molecular findings with clinically observable phenotypes such as dryness, reduced elasticity, and age-related deterioration in skin texture. This approach allowed genotype-associated differences to be interpreted in the context of downstream changes in extracellular matrix integrity, hyaluronan homeostasis, and hydration status (Rouzaud et al., 2005; Farage et al., 2008; Dai et al., 2007; Hughes et al., 2013).

Results. *MC1R* activity is a relevant determinant of cutaneous responses to ultraviolet radiation and, consequently, of biological processes associated with skin hydration. Functional *MC1R* signaling promotes eumelanin synthesis and strengthens melanocytic responses to UV damage through cAMP-dependent pathways, thereby limiting oxidative stress and enhancing

repair of UV-induced DNA lesions, whereas reduced-function alleles are associated with phenotypes such as sun sensitivity and freckling that reflect diminished photoprotective capacity (Rouzaud et al., 2005; Kadekaro et al., 2010; Bastiaens et al., 2001). In parallel, HA is a major extracellular matrix glycosaminoglycan with a central role in water binding, tissue viscoelasticity, and the maintenance of cutaneous turgor, making it highly relevant to hydration-related skin quality in both dermatologic and cosmetic contexts (Papakonstantinou et al., 2012). UVB exposure alters HA metabolism in skin, and chronic UVB irradiation can reduce dermal HA content by downregulating HA synthases while inducing compartment-specific remodeling of HA turnover, thereby providing a mechanistic bridge between reduced skin hydration, extracellular matrix disruption, visible features of photoaged skin, and impaired photoprotection (Dai et al., 2007; Averbeck et al., 2007). Taken together, these findings support the interpretation that diminished *MC1R* function may increase vulnerability to UV-driven processes that compromise HA homeostasis and contribute to dryness (Farage et al., 2008; Papakonstantinou et al., 2012).

Discussion. Taken together, the available evidence supports the view that variation in *MC1R* is relevant to the maintenance of skin hydration under conditions of ultraviolet exposure. Genotypes associated with reduced *MC1R* signaling are likely to compromise tanning efficiency and weaken cellular defense against UV-induced oxidative and DNA damage, thereby favoring cumulative extracellular matrix alterations that predispose the skin to reduced hydration quality (Rouzaud et al., 2005; Farage et al., 2008). This relationship is especially important in the context of UVB-mediated disruption of cutaneous hyaluronan homeostasis, because reduced dermal HA content compromises water retention and tissue viscoelasticity, which are essential to maintaining smoothness, suppleness, and a well-hydrated appearance of the skin (Averbeck et al., 2007; Dai et al., 2007; Papakonstantinou et al., 2012). From a mechanistic perspective, diminished *MC1R* function may thus contribute to reduced skin hydration by facilitating UV-mediated matrix injury and hyaluronan loss. This provides a biologically plausible rationale for appropriate photoprotection and, in the context of hydration-supportive skin care, for hyaluronic acid-containing interventions to support HA-dependent hydration under conditions of UVB-related stress, with both oral and low-molecular-weight topical hyaluronic acid representing complementary routes of delivery. Regular sunscreen use has direct clinical evidence for reducing skin aging (Hughes et al., 2013).

Subjects: Genetics, Beauty. **Keywords:** Genetics, Polymorphism, Beauty, Skin Hydration.

INTRODUCTION

Skin aging is a multifactorial process driven by the interplay between intrinsic determinants, including chronological aging and genetic background, and extrinsic factors, most notably ultraviolet (UV) radiation, smoking, and other environmental exposures (Farage et al., 2008). Within this framework, skin hydration is a central determinant of cutaneous function and visible skin quality.

Hyaluronic acid, or hyaluronan, is particularly relevant in this context because it contributes substantially to water retention, tissue viscoelasticity, and cutaneous turgor. The relationship between *MC1R* genotype, skin hydration and hyaluronan biology, therefore, represents a biologically plausible area of investigation. *MC1R* is of particular relevance among pigmentation-associated genes because it regulates melanocyte responsiveness to α-melanocyte-stimulating hormone (α-MSH) and thereby influences pigment production, UV sensitivity, and several non-pigmentary protective pathways, including oxidative stress control and DNA damage responses (Rouzaud et al., 2005; García-Borrón et al., 2014). In this context, the polymorphisms rs885479, rs11547464, rs1805006, and rs1805007 may be considered within a model of graded *MC1R* functional activity. Different allelic combinations are more appropriately interpreted as reflecting relatively preserved, intermediate, or reduced receptor function, with corresponding effects on the maintenance of cutaneous conditions required for normal skin hydration. This concept is especially relevant to skin hydration because insufficient photoprotection may increase susceptibility to UV-induced extracellular matrix injury and to disturbances in hyaluronic acid homeostasis, thereby compromising the structural conditions required for effective water binding and retention. Consequently, variation in *MC1R* may be relevant to hydration-related skin quality in the context of photodamage pathways that contribute to cutaneous dryness (Farage et al., 2008; Rouzaud et al., 2005; García-Borrón et al., 2014).

MC1R-MEDIATED PHOTOPROTECTION AS A DETERMINANT OF SKIN HYDRATION AND CUTANEOUS INTEGRITY

MC1R encodes a G protein-coupled receptor expressed predominantly on melanocytes. Upon stimulation by α-melanocyte-stimulating hormone (α-MSH) or adrenocorticotropic hormone (ACTH), the receptor activates adenylate cyclase, increases intracellular cyclic AMP levels, and promotes *MITF*-dependent melanogenesis, thereby shifting pigment synthesis toward eumelanin production. Because eumelanin absorbs and scatters ultraviolet (UV) radiation more efficiently than pheomelanin and is associated with a lower oxidative burden, this signaling axis represents a major determinant of cutaneous photoprotection. In addition to its relevance for pigmentation, this pathway is important because effective protection from UV exposure reduces the burden of molecular injury that can ultimately compromise extracellular matrix quality and the hyaluronic acid-dependent properties of skin suppleness and water retention, as well as for maintaining the integrity of the cutaneous microenvironment in which hydration is preserved (Rouzaud et al., 2005; Sturm et al., 2003; García-Borrón et al., 2014).

The biological relevance of *MC1R* therefore extends beyond visible pigmentation alone. A functionally competent receptor pathway enhances the melanocytic response to UV injury by facilitating repair of cyclobutane pyrimidine dimers, limiting oxidative stress, and promoting DNA damage signaling responses that preserve cellular integrity after irradiation (Rouzaud et al., 2005; Kadekaro et al., 2010; Swope et al., 2014). In this respect, *MC1R* is most appropriately viewed as an upstream regulator of cutaneous resilience to cumulative photodamage and, consequently, of the structural conditions required for effective hydration.

MC1R functional integrity is relevant to the maintenance of a cutaneous microenvironment that supports hyaluronic acid-dependent water retention and normal tissue viscoelasticity. When *MC1R*

activity is reduced, greater susceptibility to cumulative ultraviolet-induced tissue stress may favor extracellular matrix alterations that impair hydration-related skin properties, thereby contributing over time to cutaneous dryness, loss of turgor, and deterioration of overall skin quality (Bastiaens et al., 2001; Elfakir et al., 2010; Suppa et al., 2011).

FUNCTIONAL INTERPRETATION OF THE INVESTIGATED *MC1R* POLYMORPHISMS

The polymorphisms rs885479, rs11547464, rs1805006, and rs1805007 are missense variants with the potential to alter *MC1R* receptor conformation and downstream signaling behavior. Their biological consequences are not equivalent and are more appropriately interpreted as a spectrum of quantitatively or qualitatively altered receptor activity rather than a simple dichotomy of normal versus defective function. This distinction is relevant not only for pigmentary responses, but also for the degree to which cutaneous tissues remain protected from cumulative UV-induced stress that may compromise hydration-associated skin integrity.

Among these variants, certain non-favorable alleles at the investigated *MC1R* loci (rs1805006 and rs1805007) are well-established reduced-function alleles associated with diminished cyclic AMP signaling and, in some cases, impaired receptor trafficking to the cell surface, thereby attenuating melanocyte responsiveness to α-MSH and weakening adaptive responses to UV exposure (Sturm et al., 2003; García-Borrón et al., 2014). Certain non-favorable alleles of rs11547464 likewise belong to the reduced-function spectrum of *MC1R* variation, although its effect appears to involve abnormal receptor activation rather than defective membrane localization (García-Borrón et al., 2014). By contrast, rs885479 appears to have a more nuanced functional profile, with relatively preserved canonical cyclic AMP signaling in some settings, but possible effects on alternative pathways, including ERK-related signaling, and associations with specific dermatologic and melanoma-related phenotypes (García-Borrón et al., 2014; Puig-Butillé et al., 2013). Collectively, these polymorphisms can be viewed as determinants of graded susceptibility to photodamage, with downstream relevance for the maintenance of normal skin hydration.

HYALURONAN HOMEOSTASIS AS A MECHANISTIC LINK BETWEEN PHOTODAMAGE AND SKIN HYDRATION IMPAIRMENT

Hyaluronic acid, or hyaluronan (HA), is a major extracellular matrix glycosaminoglycan with a central role in water binding, tissue viscoelasticity, and the maintenance of cutaneous hydration. Its high hygroscopic capacity makes it an important determinant of skin turgor and mechanical resilience, while age-related disturbances in HA metabolism have been linked to visible deterioration of skin quality (Papakonstantinou et al., 2012).

UV exposure has been shown to alter HA metabolism in both the epidermal and dermal compartments. Acute UVB irradiation induces compartment-specific and time-dependent changes in the expression of hyaluronan synthases and hyaluronidases, whereas chronic UVB exposure is associated with loss of dermal HA and downregulation of hyaluronan synthases, changes that are consistent with matrix deterioration and dehydration (Averbeck et al., 2007; Dai et al., 2007). In addition, earlier work demonstrated that HA could undergo depolymerization following UV exposure

in solution, supporting the broader concept that radiation-induced reactive intermediates can compromise HA integrity (Rehákova et al., 1994). Taken together, these findings suggest that reduced-function *MC1R* variants may increase the likelihood that repeated UV exposure will dysregulate HA turnover, accelerate dermal matrix aging, and secondarily impair skin hydration.

MC1R VARIATION AND HYDRATION-ORIENTED PREVENTIVE STRATEGIES

At the phenotypic level, variation in *MC1R* has long been associated with traits indicative of increased ultraviolet susceptibility, including freckling, fair pigmentation, poor tanning capacity, and heightened sun sensitivity, underscoring its central role in cutaneous responses to solar exposure (Bastiaens et al., 2001). Subsequent studies extended this concept beyond pigmentary phenotype and showed that function-altering *MC1R* variants are associated with severe facial skin aging and with objective markers of periorbital cutaneous change (Elfakir et al., 2010; Suppa et al., 2011). In addition, allelic dosage appears to be relevant, as melanocytes carrying two strongly reduced-function alleles display markedly impaired α-MSH responsiveness, including weaker enhancement of ultraviolet-induced DNA repair and reduced suppression of reactive oxygen species, indicating progressively diminished biological protection as receptor function declines (Kadekaro et al., 2010).

From a preventive and supportive perspective, these genotype-dependent differences support a targeted approach to maintaining hydration-related skin quality. Broad-spectrum sunscreen remains the most evidence-based preventive measure, as long-term daily use has been shown to attenuate the progression of visible skin aging and therefore represents a key strategy for limiting cumulative ultraviolet burden in individuals with less efficient endogenous protection (Hughes et al., 2013). In parallel, hyaluronan-based interventions may serve as supportive measures within hydration-focused skin care. Topical hyaluronic acid, particularly in lower-molecular-weight formulations, has been associated with improvements in skin hydration, elasticity, and wrinkle-related parameters, while oral hyaluronan has likewise been associated with improvements in dryness- and wrinkle-related outcomes following repeated administration (Essendoubi et al., 2016; Pavicic et al., 2011; Kimura et al., 2016; Hsu et al., 2021). Together, these findings support a practical framework in which *MC1R*-informed photoprotection is complemented by hydration-supportive hyaluronan-based care.

TABLE 1: KEY STUDIES ON *MC1R*, UVB-ASSOCIATED HYALURONAN DYSREGULATION, AND HYDRATION-RELATED SKIN OUTCOMES

STUDY (AUTHOR, YEAR)	DESIGN · POPULATION · SNP	PRIMARY OUTCOME / KEY FINDINGS
Sturm et al., 2003	**Design:** Genetic association plus cell-based functional study. **Population:** Population cohort and transfected HEK293 cells. **SNP:** rs1805006, rs11547464, rs1805007, rs885479.	Showed that common *MC1R* variants differ in functional impact, supporting graded susceptibility to UV stress and therefore graded vulnerability of hydration-relevant skin quality under environmental exposure.
Elfakir et al., 2010	**Design:** Candidate-gene association study. **Population:** 530 middle-aged French women. **SNP:** rs1805007, rs885479, rs11547464, rs1805006.	Reported that common and diminished-function *MC1R* variants were associated with more severe facial skin ageing, supporting poorer preservation of hydration-related skin quality under cumulative UV exposure in carriers of reduced-function genotypes.
Puig-Butillé et al., 2013	**Design:** Genotype association study across melanoma subtypes. **Population:** Mediterranean population with melanoma. **SNP:** rs885479 highlighted; recurrent variants included, rs1805007, rs1805006, rs11547464.	Detected broad *MC1R* variation across melanoma subtypes and highlighted rs885479, underscoring that individual *MC1R* variants may exert distinct UV-responsive biological effects relevant to maintenance of skin quality.

CONCLUSION

Taken together, the available evidence supports the view that variation in *MC1R* is relevant to the preservation of skin hydration primarily because it influences the cutaneous response to ultraviolet exposure, particularly UVB-associated injury. A functionally competent *MC1R* pathway contributes to effective melanocytic photoprotection through promotion of eumelanin synthesis, oxidative stress control, and DNA damage responses, whereas reduced-function variants are associated with diminished resilience to UV-induced damage and with phenotypic features of heightened sun sensitivity (Rouzaud et al., 2005; Sturm et al., 2003; García-Borrón et al., 2014; Kadekaro et al., 2010; Swope et al., 2014). In the context of hydration biology, this is especially important because UVB exposure disrupts hyaluronan homeostasis, alters the expression of hyaluronan-regulating enzymes, and reduces dermal hyaluronic acid content, thereby compromising water retention, tissue viscoelasticity, and cutaneous turgor (Averbeck et al., 2007; Dai et al., 2007; Papakonstantinou et al.,

2012). Accordingly, the relationship between *MC1R* and skin hydration is best understood within a framework in which genetic differences in UV resilience shape the extent to which hyaluronic acid-dependent skin properties can be maintained under repeated environmental stress (Farage et al., 2008; Rouzaud et al., 2005).

Hyaluronic acid emerges from this framework as a central molecular determinant of hydration-related skin quality and a particularly important target in the prevention and management of UVB-associated deterioration in skin function and appearance. Because hyaluronan is essential to extracellular matrix hydration, suppleness, and mechanical resilience, preservation of its cutaneous homeostasis is fundamental to maintaining a well-hydrated skin phenotype (Papakonstantinou et al., 2012). The current evidence therefore supports a combined strategy in which appropriate photoprotection is used to reduce UVB burden, while hyaluronic acid-based interventions, including low-molecular-weight topical formulations and oral supplementation, help support hydration, elasticity, and overall skin quality (Hughes et al., 2013; Pavicic et al., 2011; Hsu et al., 2021). Overall, this review supports the conclusion that *MC1R*, UVB exposure, and hyaluronic acid are closely interconnected determinants of cutaneous hydration, and that their interaction is highly relevant to both dermatologic understanding and hydration-oriented skin care.

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