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REVIEW

Melanocortin-1 receptor (*MC1R*): a review for dermatologists

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ABSTRACT

Melanocortin-1 receptor (*MC1R*) and its variants have a pivotal role in melanin synthesis. However, MC1R has been associated to non-pigmentary pathways related to DNA-repair activities and inflammation. The aim of this review is to provide an up-to-date overview about the role of MC1R in the skin. Specifically, after summarizing the current knowledge about MC1R structure and polymorphisms, we report data concerning the correlation between MC1R, phenotypic traits, skin aging, other diseases and skin cancers and their risk assessment through genetic testing.

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KEY WORDS: Human MC1R protein; Melanoma; Skin aging; Skin neoplasms.

The *MC1R* (melanocortin-1 receptor) gene codifies for a seven pass transmembrane G protein coupled receptor with a pivotal role in melanogenesis. Importantly, *MC1R* is a highly polymorphic gene, with over 300 polymorphisms (or variants) described.[1, 2]

Some of these polymorphic variants have been related to the red hair color (RHC) phenotype, being characterized by red hair, freckles, fair skin and impaired tanning ability and to an increased risk of skin cancers.[3-6]

MC1R is expressed on different cell types in the skin, however its expression and functional role have been described on melanocytes, while functions on other cell types have been debated and have yet to be clarified.[2, 7] *Mc1r* shows a high affinity for α-melanocyte-stimulating hormone (α-MSH) and lower for ACTH,[8, 9] both hormones deriving from the cleavage of pro-opiomelanocortin.[10] Binding of α-MSH to *Mc1r* activates the receptor and stimulates eumelanin synthesis, therefore mediating the tanning ability of an individual.[11, 12]

Interestingly, in the last two decades, the role of MC1R in DNA-repair has emerged, thus contributing to explain the link between MC1R variants, skin photodamage/photoaging and skin cancer development.[13, 14]

Due to the important role of MC1R in the skin, and recent reviews available on the biologic aspects of the receptor,the aim of this review is to summarize basic mo-

lecular knowledge of the receptor for Dermatologists and updated information on the role played by MC1R polymorphisms in skin cancers.

Basic knowledge about MC1R structure and functions

MC1R structure and functions have been recently revised[2, 7, 15] and main findings are summarized herein.

MC1R structure

MC1R gene (16q24.3) codifies for a 317 amino acid, seven transmembrane (TM) G protein-coupled receptor, with a N- and C-terminal[16-20] (Figure 1). Extracellular N-terminal shows a glycosylation site, while intracellular C-terminal carries a palmitoylation site, which is important for functional regulation of the receptor.[18-20] Recently, a calcium-binding site has been described close to the TM domain 3, on the extracellular side, and calcium has been shown to be crucial in ligand binding to the receptor.[21]

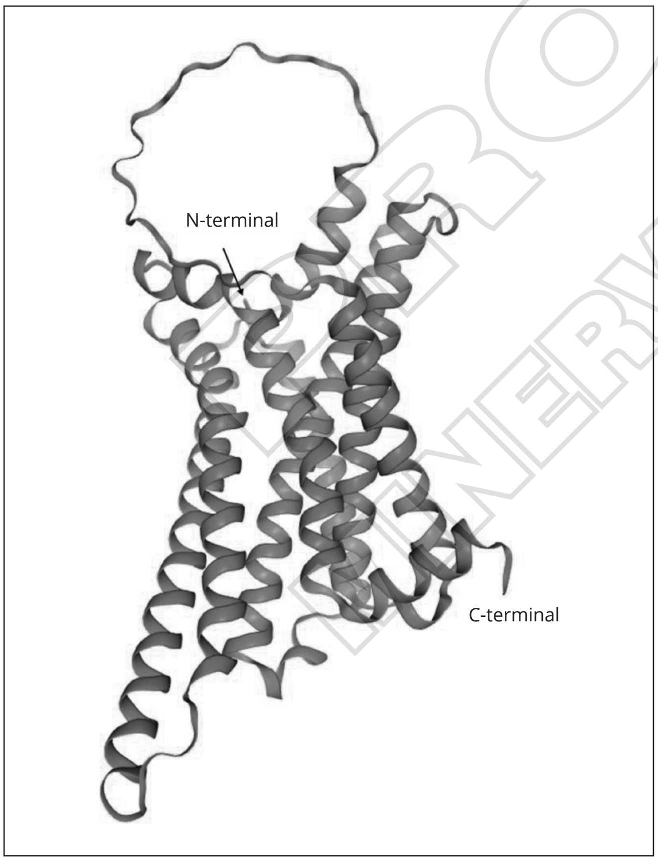

Figure 1.—*Mc1r* structure.

MC1R functions

MC1R displays a constitutive activation, not related to the agonist binding.[22] However, MC1R can be activated after stimulation with its agonists, with the main one being represented by α-MSH.[23] Of note, the release of α-MSH has been related, among the others, to UV exposure, which induces α-MSH realease from keratinocytes.[24]

Additionally, inverse agonists competing with MC1R agonists and decreasing the constitutive signaling of the receptor have been described, together with paracrine factors and intracellular molecules contributing to MC1R signaling regulation.[2]

MC1R has a key role into pigmentary as well as non-pigmentary activities in the skin. The most studied downstream signaling activated by α-MSH /MC1R is the cAMP pathway. The signaling related to cAMP pathway involves adenylyl-cyclase activation, leading to increased levels of cAMP and to CREB phosphorylation by protein kinase A (PKA). As a consequence, the upregulation of the microphthalmia-associated transcription factor (MITF) leads to increased tyrosinase (TYR) activity, showing a key role in melanin production.[25-32] Melanin is sythetized within specific organelles called melanosomes, which are then transferred to keratinocytes[12] (Figure 2). It is well known that melanocytes and associated keratinocytes have a symbiotic relationship and constitute the so called epidermal melanin unit.

Actually, two types of melanin exist: red pheomelanin and black eumelanin. Eumelanin is photoprotective but pheomelanin may contribute to UV-induced skin damage by generating free radicals upon UV radiation. Interestingly, UV exposure triggers α-MSH synthesis in keratinocytes, activating MC1R on melanocytes to produce melanosomes, which are then transferred back to keratinocytes to shield the nucleus from UV radiation (Figure 3, 4). α-MSH/MC1R leads to the shift from the pro-oxidant pheomelanin (red-yellow) to the anti-oxidant eu-

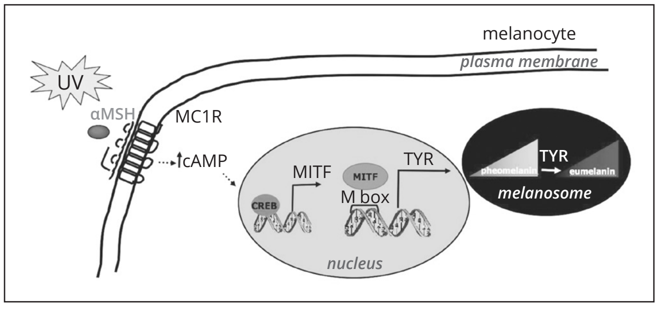

Figure 2.—α-melanocortin stimulating hormone/Mc1r signaling.

melanin (brown-black) production, resulting in tanning ability.[11, 12, 33, 34]

Additionally, cAMP pathway has been involved into other important non-pigmentary protective responses to UV exposure which are the development of increased epidermal thickness[35] and the enhancement of nucleotide excision repair, contributing to DNA repair activity.[19]

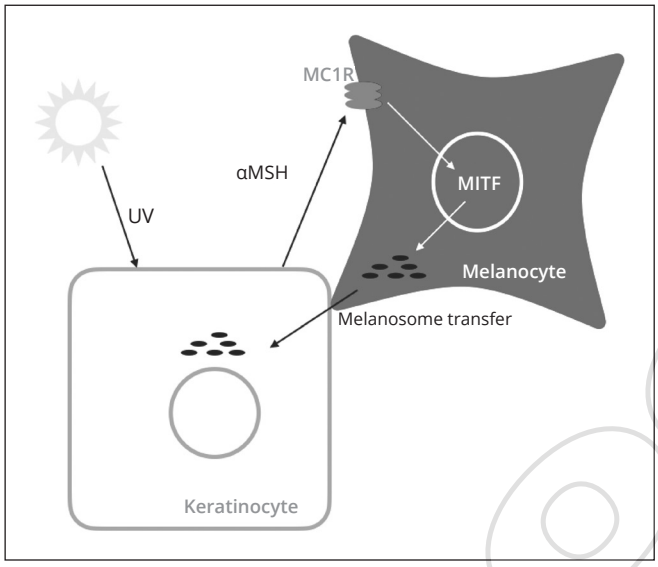

Figure 3.—MC1R pigmentary pathway. Ultraviolet (UV) activating keratinocytes producing α-melanocortin stimulating hormone (α-MSH), binding Mc1r located on melanocytes surface. Upon α-MSH/Mc1r signaling activation, pigment production increases in melanocytes and melanosomes are transferred to keratynocyte to protect DNA from UV damage.

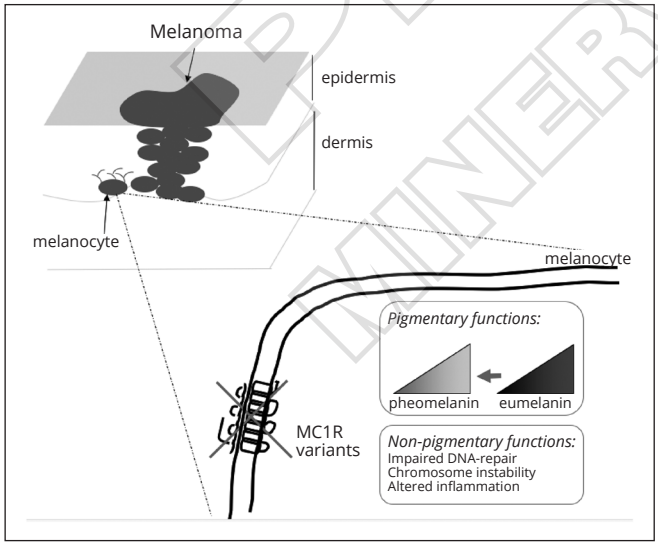

Figure 4.—MC1R variants lead to impaired pigmentary and non-pigmentary functions, associated with melanoma development.

Other downstream signaling pathways to MC1R involve complex interactions with phosphoinositide 3-kinase (PI3K) / AKT pathway, nucleotide excision repair system, ERK pathway, transactivation of the receptor tyrosine kinase c-KIT, peroxisome proliferator-activated receptors, catalase, TNF-α-stimulated NF-κB transcription factor, Nuclear factor (erythroid-derived 2)-like 2 (Nrf2). These pathways have been implicated in DNA repair, chromosome stability, antioxidant activities, melanocyte homeostasis, survival, migration and differentiation, senescence and inflammation.[2, 7]

Other additional important pathways implicated downstream MC1R include autophagy. Autophagy genes (ATG12, ATG2A, ATG9A, ATG7) were detected downderegulated in healthy skin from RHC individuals.[36] Autophagosome formation play a role in melanosome formation and destruction of abnormal melanosomes. Cutaneous cells from RHC individuals show over-expression of GABARAPL2, which is essential for autophagosome maturation and down-regulation of CLN3 which play a role in autophagy, endocytosis and vesicular trafficking.[36]

MC1R polymorphisms and their impact on skin phenotype

Over 300 *MC1R* polymorphisms have been described.[1, 2] These variants have been associated to different degrees of MC1R function impairment and show a diverse geographical distribution. From the evolutionary point of view, while *MC1R* variants are less common in Africa, they are tolerated in Europeans and East Asian populations, where they facilitate vitamin D production in response to UV exposure. Indeed, vitamin D production is important in bone health, therefore keeping reproduction capacity and preservation of the species.[37]

MC1R polymorphisms have been classified according to the penetrance of the RHC phenotype (red hair, freckles, fair skin and impaired tanning ability) into strongly associated RHC variants, weaker ones — called "r" alleles — and those not impairing the receptor functions.[38] Main MC1R polymorphisms, both RHC and r, are involved in the synthesis of hypomorphic protein receptors, with impaired activation of downstream signaling.[39] RHC variants include R151C, R160W, D84E — showing reduced cell surface expression — and D294H and R142H — with normal surface expression but decreased ability to bind the ligand.[40-43] In addition, r variants include V60L, V92M,

and R163Q, showing intermediate cell surface and overall estimated function variation controversial since either minor or no impairment have been described.[35, 40, 44]

MC1R can be considered the main gene contributing to red hair, although *MC1R* polymorphisms may have a dosage effect for both skin and hair color. Therefore, different shades of red hair color have been associated to carriers of RHC, while V60L has been described as a low-penetrance "red hair and fair skin" allele, also associated to blonde hair.[45, 46]

However, after the initial classification of these variants, many additional polymorphisms have been described and, although less common, their functional impact has not been evaluated in all cases.

MC1R and phenotypic characteristics

MC1R has a key role in pigmentation, showing its influence in phenotypic characteristics, above all in determining skin and hair color. As widely reported in the literature, the RHC phenotype has been associated with *RHC* variants. This RHC phenotype is characterized by red hair, fair skin, freckles, and reduced tanning ability.[47-49]

MC1R can be considered the main gene contributing to red hair, however it is possible that patients showing red hair may carry a wt *MC1R*, therefore leading to the hypothesis that this phenotypic trait may also be associated to mutations in other genes, such as POMC.[47] Apart from the specific *MC1R* variant, *MC1R* polymorphisms may have a dosage effect for both skin and hair color. Therefore, different shades of red hair color have been associated to homozygotes or compound heterozygotes — mainly for RHC variants and 86insA, 537insC — status, as compared to heterozygote individuals,[45] while V60L has been described as a low-penetrance "red hair and fair skin" allele, also associated to blonde hair.[46] Similarly, different degrees of tanning ability have been described in carriers of two variant alleles, as compared to wt subjects.[35] Additionally, tanning ability has been shown to be different in *MC1R* RHC female carriers, as compared to males.[50]

A single study reported a correlation between *MC1R* variant and eye color in a cohort of 1679 patients with primary melanoma, specifically the R142H with blue/green eye color.[51]

MC1R and skin photodamage and photoaging

MC1R variants have been associated to skin photoaging.[52-54] Interestingly, non-invasive skin imaging revealed the underlying skin variations in photo-exposed skin of *MC1R*-variant carriers, as compared to non-RHC subjects.[53] *MC1R* RHC carriers showed heterogeneous distribution of pigmentation, different collagen morphology and increased vessels amount, as compared to non-RHC individuals.[53] These features have been then related to the two types of skin photoaging, atrophic and hypertrophic, as described by Sachs *et al.*[54] In particular, atrophic skin photoaging, characterized by dyspigmentation, sagging skin and telangiectasia and tendency to develop actinic keratoses has been associated with *MC1R* main polymorphisms, as compared to controls subjects and those showing hypertrophic skin photoaging.[55]

MC1R and nevi

Whether *MC1R* polymorphisms have an association with the number and size of nevi remains controversial, due to contradictory results in the current literature. These results suggested that nevi development and growth may have multifactorial underlying mechanisms.[56, 57] However, recently, *MC1R* r variant V60L has been proposed as an independent predictor of nevus count, above all in women, in a study involving 494 subjects.[58]

Overall, a link between *MC1R* variants and nevus phenotype has been described. In particular, while non-RCH carriers showed, at dermoscopy, an increased number of colors, streaks, and pigmented network, RHC-carriers had overall hypopigmentation or "white" nevi with fewer dermoscopic structures or eccentric pigmentation.[59-62]

Furthermore, patients with previous multiple melanomas carrying *MC1R* variants and CDKN2A mutations, showed, at RCM, roundish cells infiltrating the dermo–epidermal junction.[61]

MC1R and skin cancers

The association between *MC1R* variants and skin cancers, particularly melanoma, has been widely proved through genome-wide association studies and meta-analyses.[63-66]

Both pigmentary as well as non-pigmentary functions of MC1R have been implicated into skin cancers development.[7, 15, 67]

MC1R and melanoma

Over the last two decades, the association between *MC1R* variants - particularly RHC - and melanoma risk has been described and supported by studies across different populations and large cohorts across the world.[15, 63-66]

In detail, the number of *MC1R* variants were positively associated with increased risk of melanoma. Accordingly, a pooled analysis in a large cohort of 3830 melanoma pa-

tients and 2619 control subjects showed that the presence of any *MC1R* variant had a direct effect on melanoma, giving a 60% higher risk to carriers versus non-carriers.[11] Overall, it has been estimated a 2-fold increased risk of melanoma in subjects with a single *MC1R* variant and up to 6-fold increased risk in carriers of 2 or more variants.[67-71]

Interestingly, patients with darker skin phototypes showed a significant risk of melanoma in association with *MC1R* variants, as compared to fair skin types. These findings underline how pigmentary and UV-dependent *MC1R* functions can partially explain the risk of melanoma. Indeed, the correlation between *MC1R* and melanoma in darker skin phototypes highlighted the crucial role of non-pigmentary mechanisms in melanoma development.[4, 5, 66-68, 72] Furthermore, interactions with CDKN2A mutations, a known risk factor for melanoma, should be considered as an additional factor contributing to increase melanoma risk in MC1R variant carriers.[15]

Interestingly, a correlation between MC1R variants and demographic characteristics, such as age and sex, have been described. While the correlation of MC1R and age at diagnosis for melanoma is still unclear,[71] MC1R r variants have been proven a role in melanoma development in childhood and adolescents.[73] Furthermore, MC1R has been reported as an independent risk factor for melanoma in females and better overall survival rates for melanoma were observed in female patients, as compared to males.[74, 75] Additional factors contributing to melanoma-specific survival were the number of MC1R variants[76] or the presence of BRAFV600 mutation.[77]

Another interesting correlation has been highlighted between MC1R variants, melanoma location and type. RHC and r MC1R polymorphisms have been associated with melanomas on intermittent as well as on chronic sun exposed areas,[4, 71, 78-80] and with with all melanoma types except the acral lentiginous. Specifically, R163Q MC1R variant has been associated with lentigo maligna melanoma in a Mediterranean population of 1679 patients with primary melanoma, independently from skin phototype.[51]

Similarly, to what has been previously described for nevi, MC1R variants – particularly RHC – have been associated with colors and dermoscopic patterns of melanoma. In detail, a/hypopigmentated or "red" melanomas, fewer dermoscopic structures and lower values of the ABCD Total Dermoscopy Score have been described in MC1R RHC carriers, as compared to non-RHC.[59-61, 81] Therefore, due to the lack of pigmentation and structureless areas, melanomas in MC1R variant carriers have been defined as difficult-to-interpret by dermoscopy alone.[60, 82]

MC1R and NMSC

Considering the role of MC1R on phenotypic characteristics and its modulation of oxidant activities, DNA repair and inflammation, the association between MC1R variants and NMSC has been investigated.

MC1R RHC variants have been found to have a two- to threefold increased risk of developing NMSCs — including basal cell and squamous cell carcinomas — as compared to WT,[82, 83] independently from skin phenotype.[11] Increased risk of NMSCs has also been associated with two or more MC1R variants.[71]

MC1R and other diseases

The role of MC1R variants has been also investigated a pigmentary disorder, such as vitiligo; however, MC1R variants were not significantly associated with the disease.[84, 85] Despite this lack of association, a different MC1R expression has been described between affected and surrounding skin, showing a lower and higher Mc1r expression, respectively, as compared to skin in healthy subjects.[85-87]

Additionally, due to the role of MC1R in inflammation, the distribution of its variants has been preliminary explored in psoriasis, highlighting, on a small cohort, a negative correlation between MC1R variants and the disease.[88] This negative correlation is not surprising, considering that a protective role of psoriasis for melanoma development has been previously reported.[89]

Being MC1R also expressed in central nervous system, *MC1R* variants have also been implicated in disregulation of several neurological pathways,[90] that can explain the association between RHC *MC1R* variants and Parkinson disease risk,[91] non red hair variant V92M with Alzheimer[92] and RHC *MC1R* variant with decrease in the age of onset of Huntington desease.[93]

MC1R testing and skin cancer prevention

Despite the widely proven role of *MC1R* polymorphisms in skin cancer risk, independently from skin phenotype characteristichs, the impact of *MC1R* genetic testing has been limited in current practice, to date. However, in the last couple of years, many studies have explored the impact of *MC1R* testing in the general population and in subjects with high and average risk of skin cancers, as compared to controls.

In the general population, a randomized control trial (RCT) enrolling 499 patients explored the intest to perform *MC1R* testing after giving information about risks and benefits of the test. Mostly, persons involved were non-Hispanic White, showed a low-average school education and experienced sunburns. However, only a small amount of people were considered at high-risk to develop skin cancers. Of note, people with a history of previous sunburns significantly requested the test more than other subjects enrolled.[94]

Another potential aspect that might limit the widespreading of *MC1R* testing is that people with low health literacy education might need help in understanding the result of genetic test.[95]

As a matter of fact, to test the comprehension of genetic risk in the general population, a RCT involving 145 participants replying to open-ended questions concerning their reaction to *MC1R* testing, 2 weeks after receiving the result was performed. Overall, more than one half of both average and higher-risk participants showed comprehension of results, one third gave ambiguous replies while remnant showed miscomprehension of either the aim of the test or the meaning of the test.[96]

A recent RCT Involving 1134 non-Hispanic White subjects explored cognitive responses to generic or precise prevention material including *MC1R* genetic risk. Interestingly, moderate intention to change preventive measures for melanoma has been reported in subjects reading most of the prevention material incorporating *MC1R* genetic risk (higher/average) or generic prevention (standard) material. Personal defensive reactions have been reported in higher risk participants, as compared to average risk and control participants. This behavioral reaction seem to justify the lower clarity, and risk recall observed in higher risk patients, as compared to the other subjects involved in the study.[97] However, when *MC1R* testing was performed in patients with previous history of non-melanoma skin cancers, results revealed that they were receptive to genetic information and half the patients involved found the test important.[98] Similarly to what have been previously reported for the general population, almost half of patients involved in the study logged onto the website to read information about *MC1R* testing, then proceeding with the test.[98] Interestingly, two weeks after receiving the genetic feedback, patients read the entire report, showing high comprehension and satisfaction for the feedback, associated with low distress, and predominance of positive emotional outcomes. Additionally, patients took the occasion to share information within their families and to talk with their physicians.[98] Furthermore, the role of genetic testing for *MC1R* on skin cancer risk perception and increased sun protection attitude was proved when combining UV photographs plus MC1R testing.[99]

Therefore, *MC1R* testing can be considered as a part of the process leading toward personalized medicine. This process encompasses the role of physicians that should give appropriate support to patients, considering different personal health literacy skills, to limit the potential distress that can come from understanding the increased risk of cancers based on the results of genetic tests.

Conclusions and perspectives

The *MC1R* gene codifies for a seven transmembrane G protein-coupled receptor and it is highly polymorphic. *MC1R* has a pivotal role in pigmentary traits in humans, being implicated in hair and skin color. It has therefore an important influence on phenotypic traits of patients that should be recognized by Dermatologists. Additionally, recent insights into skin photoaging types by *MC1R* polymorphisms has emerged and further studies will aim to provide additional information into the pathogenetic correlation between skin photoaging and skin cancer. Importantly, *MC1R* has been implicated in DNA repair activity, authophagy and chromosome stability, unrevealing underlying mechanisms relating *MC1R* polymorphisms and skin cancer development.

However, despite the consolidated knowledge relating this genetic polymorphism to skin cancers, the role of *MC1R* testing has yet to be clarified. In the last two years, some RCT across different populations revealed the supportive role of doctors in giving appropriate information about *MC1R* testing to patients.

Taken together, these data highlight how important it is to further investigate MC1R functions and to spread knowledge about this gene amongst Dermatologists first and then to educate patients.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Stefania Guida, Susana Puig, and Chiara Di Resta have given substantial contributions to the conception or the design of the manuscript. Fabio Sallustio, Eleonora Mangano, and Giorgio Stabile have performed data acquisition, analysis and interpretation. All authors have participated to the drafting of the manuscript. Caterina Longo, Giovanni Pellacani, Gabriella Guida, and Franco Rongioletti revised it critically. All authors read and approved the final version of the manuscript.

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