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Is Mc1r an important regulator of non-pigmentary responses to UV radiation?

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Abstract

MC1R is recognized for its role in the regulation of melanin pigmentation. In addition, many investigators believe that it also plays a crucial role in immunomodulation (immunosuppression) and in melanogenesis-independent protective responses against ultraviolet radiation (UVR). Surprisingly Wolnicka-Glubisz *et al* have shown that loss of function in the MC1R has no effect on inflammatory responses and immunosuppression induced by UVR in C57BL/6 mice as well as on the degree of UVA-induced DNA damage in the epidermis and dermis. These findings, by challenging the existing dogmas on the precise role of MC1R in non-pigmentary responses to the UVR, mandate further research to either validate the presented data or to define to which degree these phenomena are restricted to the C57BL/6 mouse model or are applicable to other species including humans. The alternative target for immunomodulation is represented by MC3R. However, cutaneous expression of MC3R remains to be demonstrated.

Keywords

MSH; UVR; MC1R; immunosuppression

Commentary

POMC derived peptides including MSH and ACTH and the melanocortin receptor type 1 (MC1R) are recognized for their role in the regulation of melanin pigmentation (1, 2). In addition, MSH plays an important role in immunomodulation including induction of anti-inflammatory responses with an assumption that this pathway is mediated through activation of MC1R (3–5). However, in the recent review paper by Bohm & Grassel (3) it is already envisioned that MC3R is a target for mediation of anti-inflammatory effects by MSH and related peptides in the osteoarticular system. It is also believed that MSH activation of MC1R induces protective mechanisms against damaging effects of ultraviolet radiation (UVR) (6, 7).

Most recently, researchers from George Washington and Jagiellonian Universities, using C57BL/6-c, C57BL/6 and C57BL/6-Mc1r^{e/e} mouse strains, have made surprising finding

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Conflicts of Interest

There are no conflicts of interest to declare for all the authors

that loss of function in the MC1R has neither impacted inflammatory responses to UV nor affected UVR induced immunosuppression (8). These findings are in striking contrast with generally accepted opinion that constitutive or ligand induced MC1R activity plays an important role in modulation of cutaneous immune activity in response to UVR (3–5). Interestingly, the authors also showed that UVR induced similar DNA damage in the epidermis and dermis irrespectively of the genetic background of these mouse strains. These surprising findings challenge the existing dogmas on the precise role of MC1R in non-pigmentary responses to the UVR (3–7) (Fig. 1).

These experiments also rise several questions. It was recently reported that effects of melanocortins on DNA repair and diminishing of oxidative stress caused by UV irradiation is mediated by MC1R and requires activity of p53 (7, 9). In addition, recent study has shown that MSH bound to the MC1R 1 activates adenylate cyclase activity with following activation of Xeroderma pigmentosum group A (XPA)-binding protein 1 and its nuclear translocation, a critical factor controlling nucleotide excision repair signaling pathways (10). Also, the presence of thymine dimer in UV irradiated skin might not be ideal proof of non-essential role of MC1R receptor in UV response. Therefore, it would be interesting to observe how the murine skin with selected MC1R phenotypes copes with DNA damage and somatic mutations. It must also be noted that polymorphism of MC1R is recognized as one of the skin cancer-risk factors (11).

Although the immunoregulatory role of MSH is unquestionable (3–5), there are several studies showing that MC1R is not essential for immunomodulatory function of melanocortins. Getting et al (12) showed that the presence of fully functional MC1R receptor is not essential for inactivation of peritoneal macrophages by MSH, but the effect was abrogated by selective MC3R/MC4R antagonist SHU9119, but not by the selective MC4R antagonist HS024 and, consequently MC3R agonist inhibited peritoneal macrophages. Other study showed that MC3R, but not MC1R is essential for abrogation of urate-crystal-activated inflammation in rat model of arthritis (13). Moreover, Cooper et al (14) showed that immunosuppressive effects of MSH on streptokinase streptodornase-induced lymphocyte proliferation in human, was not dependent on MC1R allelic variations. They also postulated that presence of MC3R might be required for immunomodulatory activity of MSH. In contrast Li and Taylor (15) showed that MC1R receptor is essential for effective inhibition of NO generation as well as TNF production by -MSH in lipopolysaccharides (LPS)-stimulated RAW264.7 macrophages. Nevertheless, authors also found that RAW264.7 macrophages express MC3R but not MC5R and suggested that MC3R might also be involved in anti-inflammatory response but through non-TLR pathways (15). The same cellular model was used to demonstrate that MC1R is essential for inhibition of LPS induced inflammation as well as 2-chloro-1,3,5-trinitrobenzene (TNCB)-induced atopic dermatitis model and this observation was confirmed by in vivo studies(16). Furthermore, Loser et al have convincingly demonstrated an important role of -MSH and MC1R in MHC class I-restricted cytotoxicity (17).

Thus, striking observation by Wolnicka-Glubisz et al (8) can be explained by involvement of other members of melanocortin receptor family, e.g., MC3R or perhaps MC5R. MC3R is thought to interact mainly with MSH with EC50 of 7 nM, but according to the binding efficiency studies MSH and ACTH could bind to MC3R with comparable affinity with EC50 at 1 and 6 nM, respectively (See (3) for review). MC3R may be involved in activation of steroidogenesis (18) and food intake, but interestingly, *Mc3^{-/-}* mice show selective upregulation of IL-1, IL-6, and *Nos2* when compared to wt mice (19). Thus, activation of MC3R may represent an alternative pathway for melanocortin induced immunosuppression (Fig. 1). However, cutaneous expression of MC3R remains to be demonstrated.

As discussed by Li and Taylor (15) activation of anti-inflammatory response by melanocortins might depend on the specificity of induction inflammatory factors and MC1R may be essential for attenuation of LPS-induced, TLR4-activated immune responses, while inhibition of urate-crystal-activated inflammation requires MC3R activity and is not affected by MC1R downregulation. It has to be underlined that the observed effects might also reflect cell type or organism specific differences in the regulation of immune response or genetic variations. In fact, the authors analyzed the selected population of CD11b+Ly6G+ cells (8). Also the C57BL/6 background may not be ideal to extrapolate the findings to other rodent species. For example, while the important role of POMC derived peptides in regulation of melanin pigmentation is demonstrated in vast majority of rodent species (1, 20), the POMC^{-/-} C57BL/6 mice produce solely eumelanin pigment because of recessive (a/a) genetic background (21). Finally, there are significant difference in human and rodent (nocturnal specie) skin, which includes differences in local neuropeptide signaling (2, 22). Thus, further research is necessary to validate the presented data or to determine to which degree these phenomena extend beyond the C57BL/6 mouse model.

Taken together, recently published studies including Wolnicka-Glubisz et al paper (8), brought additional level of complexity to the model of MSH regulatory functions on immune responses indicating that MC1R might not be its only target in the skin and implying MC3R as an additional target triggering alternative pathways leading to immunosuppression (Fig. 1). Furthermore, Wolnicka-Glubisz et al findings (8) challenge the existing dogma that MC1R is crucial and/or very important in non-pigmentary responses to the UVR, which should stimulate further studies in this area.

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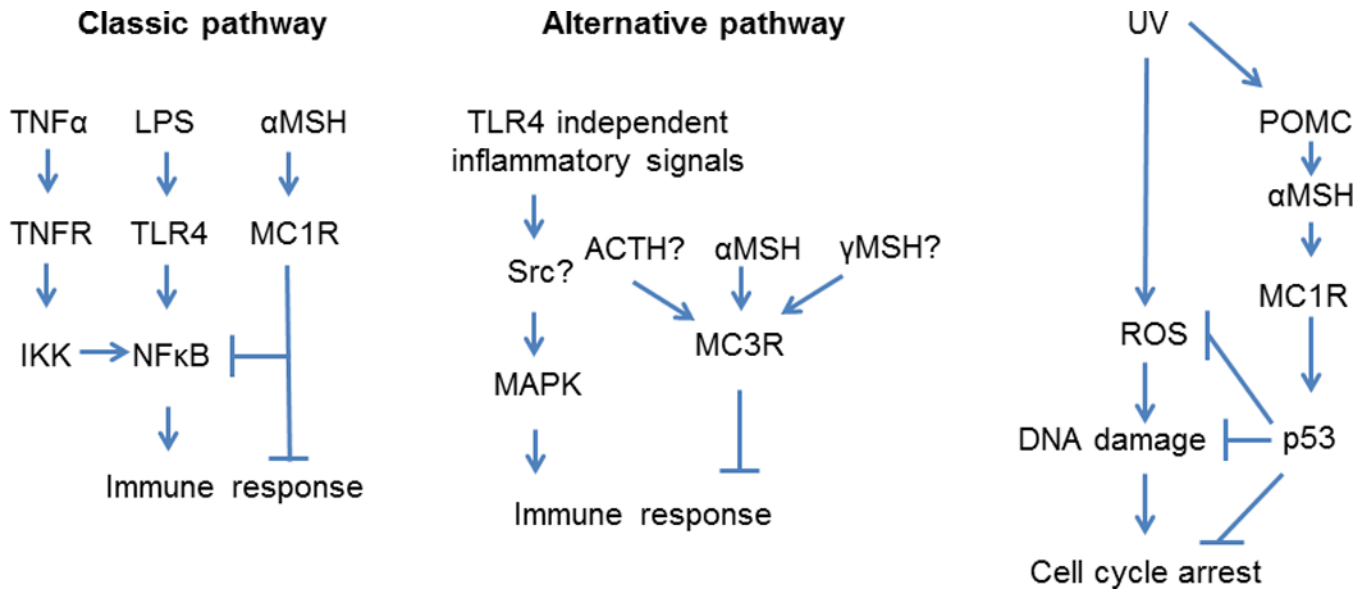


Figure 1. Classic and alternative pathways involved in UVR-induced non-pigmentary responses mediated by melanocortins.