Suppression of Melanogenesis by Induction of Endogenous Intracellular Antioxidant in Human Melanocytes

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Abstract

Ultraviolet (UV)-induced melanogenesis is caused by several types of melanogen, which are released in skin following UV radiation. Among them, nitric oxide (NO) has recently been shown to function as a potent mediator. Metallothionein (MT), which functions in metal homeostasis and metal detoxification, also acts as an intracellular antioxidant that has been reported to scavenge NO. We investigated the existence and induction of MT in melanocytes, and its inhibitory effect on NO-induced melanogenesis. MT expression was detected in melanocytes, however, at a lower level than in keratinocytes and fibroblasts, and its induction was possible with the addition of zinc chloride and dexamethasone. Further, an NO-stimulated increase of tyrosinase activity in melanocytes was remarkably suppressed when MT was induced prior to NO stimulation, and the same suppressive effect of melanogenesis was observed when α-melanocyte stimulating hormone and endothelin-1 were used as stimulators, during which the degree of suppression corresponded to the level of induced MT protein. Next, to study the mechanism of melanogenesis inhibition by MT, its effects on tyrosinase expression and the direct inhibition of tyrosinase were also examined. Changes in tyrosinase protein expression were not observed in melanocytes, even when MT was induced, while the suppressive effect of MT induction toward increased tyrosinase activity was neutralized by the addition of anti-MT antibody to the melanosome fraction. Further, purified human MT showed an ability to inhibit tyrosinase activity in melanocytes. Our results demonstrated that MT induction may be effective to suppress melanogenesis stimulated by NO as well as other melanogens, and this suppressive effect might be due to a direct inhibition of tyrosinase activity by the induced MT.

Key words: metallothionein, intracellular antioxidant, tyrosinase, melanogenesis.

1. はじめに

メラニンは生体防御のために必要に応じてメラノサイトが産生し、ケラチノサイトに転送され皮膚全体を紫外線から守る。紫外線の刺激がなくなれば、肌は自然にメラニンを排出し元の状態に戻る。ところが、このメラニンの生成と排出のバランスが崩れるとシミとなって現れてしまう。シミ形成のメカニズムはまだ明らかではないが、紫外線による色素沈着過程に原因があると考えられる。

このような現状のなか、メラニン合成を抑制する方法としては、チロシナーゼ活性を選択的に阻害する方法や、メラノサイトを刺激する因子の産生を抑えたり、働きを阻害したりする方法が試みられている。

本論では、メラノサイトの内因性抗酸化物質を高めることによるメラニン合成抑制方法について述べる。

2. 紫外線による色素沈着

紫外線により色素沈着が起こるメカニズムは、以前は紫外線が直接メラノサイトを活性化すると報告されていたが、近年の報告では紫外線によりケラチノサイト等の細胞が種々の刺激因子を産生し、メラノサイトを活性化するためと考えられるようになった。これらの刺激因子としては、メラノサイト刺激ホルモン