On the basis of the finding that the homeostasis of dermal DCs can be modulated by epidermal keratinocytes, it is tempting to speculate that interaction between the epidermis and DC may be one of the mechanisms that integrates the dermal immune system. Further studies are necessary to understand how this mechanism works under physiological conditions and whether it fails in certain skin disorders, such as psoriasis, where the amount of TGFβ1 is correlated with the severity of the disease (Kallimanis et al., 2009). Normalizing keratinocyte/DC interplay through TGFβ1 may be a novel therapeutic approach for psoriasis and related inflammatory skin diseases.

The study by Mohammed et al. (2012) provides new insight into cutaneous biology. To further understand its significance, it will be interesting to address whether transient induction of TGFβ1 has other effects, in addition to promoting immune responses. As DNFβ, which Mohammed et al. used to induce contact hypersensitivity, is a hapten with strong immunogenicity, the enhanced response in the presence of transient TGFβ1 induction during sensitization could have been influenced by the inflammatory cytoplasmic organelles called melanosomes, synthesized in melanocytes, stored in cytoplasmic organelles called melanosomes, and providing protection against UV-induced damage by absorbing and scattering UV radiation (reviewed in Park et al., 2006).

REFERENCES


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Cutaneous Pigmentation in Health and Disease: Novel and Well-Established Players

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Cutaneous pigment formation and aberration in disease are addressed. Dynoodt et al. (this issue) present data on a specific micro RNA that downregulates proteins involved in melanogenesis and melanosome movement. Kim et al. (this issue) present data showing that Wnt signaling is involved in the pathogenesis of melasma. Both articles enhance our understanding of cutaneous pigmentation and point to targets in the development of novel therapeutic modalities.


Melanin is a complex biopolymer that is synthesized in melanocytes, stored in cytoplasmic organelles called melanosomes, and provides protection against UV-induced damage by absorbing and scattering UV radiation (reviewed in Park et al., 2006).

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Melanogenesis, the synthesis and distribution of melanin in the epidermis, involves several steps: transcription of proteins required for melanogenesis; melanosome biogenesis; sorting of melanogenic proteins into melanosomes; transport of melanosomes to the tips of melanocyte dendrites, and transfer of melanosomes to keratinocytes. Disruptions in any of these events may result in hypopigmentation or hyperpigmentation. Melanin synthesis is largely influenced by UV radiation, as well as by positive and negative signals from neighboring keratinocytes and to a lesser degree from dermal fibroblasts.

As is true of cellular constituents, melanin synthesis and transfer to keratinocytes is controlled by an array of genes whose transcription leads to mRNA synthesis. mRNAs carry coding information to ribosomes where protein synthesis takes place. mRNAs are partly regulated by micro RNAs (miRNA), which are small post-transcriptional molecules that bind to complementary sequences on mRNAs and affect mRNA stability and translational capacity (Elbashir et al., 2001).

Tyrosinase, the enzyme that catalyzes the first two steps in melanin biosynthesis, is the rate-limiting enzyme in melanin biosynthesis, and it resides within melanosomes. Tyrosinase-related protein 1 (TRP-1), an enzyme that is structurally related to tyrosinase, is complexed with tyrosinase within the melanosomes and likely affects tyrosinase activation and/or stability. Tyrosinase and TRP-1 transcription is partly upregulated by the nuclear transcription factor microphthalmia-associated transcription factor (MITF), which also enhances melanocyte survival (reviewed in Park and Yaar, 2012). MITF transcription is upregulated by the transcription factor SOX9 (Figure 1). Another important regulator of MITF transcription is α-melanocyte-stimulating hormone (α-MSH), a naturally occurring endogenous peptide hormone that binds to its melanocortin receptor-1 (MCR-1) on melanocytes to induce a signal transduction pathway leading to increased cellular cAMP and resulting in MITF transcription (Figure 1; reviewed in Park and Yaar, 2012). Interestingly, it is possible to increase intracellular levels of cAMP independent of α-MSH and MCR-1 using forskolin, an organic compound produced by the Indian plant Coleus forskohlii (Figure 1; D’Orazio et al., 2006). Thus, forskolin is an MITF transcription modulator. MITF transcription is also upregulated by the Wnt family of proteins. These extracellular signaling molecules bind to Frizzled receptors and induce intracellular signal transduction pathways that result in MITF transcription (Figure 1; reviewed in Park and Yaar, 2012). Conversely, Wnt proteins are inhibited by a secreted lipid-binding protein called Wnt inhibitory factor-1 (WIF-1) (Hsieh et al., 1999), which is primarily of keratinocyte and fibroblast origin (Gudjonsson et al., 2010). By binding Wnt proteins, WIF-1 interferes with their activity and consequently inhibits MITF transcription.

An important part of cutaneous pigmentation is the transfer of melanosomes to keratinocytes. This requires proper melanocyte dendrite formation and proper transport of melanosomes to
the tip of the dendrites. Actin is a major structural component of melanocyte dendrites, and actin filament disruption leads to dendrite loss. Fascin homolog 1 (Fscn1) is a protein that assists in organizing filamentous actin into bundles, and thus is crucial for dendrite formation (Duh et al., 1994). Within each dendrite, melanosomes are attached to microtubules, cylindrical polymers of tubulin that are important components of the cytoskeleton. Melanosomes move bidirectionally along these microtubules within dendrites, and their movement is facilitated by two motor proteins that are attached to the melanosome and to the microtubules (reviewed in Park and Yaar, 2012). Centrifugal, anterograde melanosome movement is primarily mediated by the motor protein kinesin, whereas their centripetal, retrograde movement is controlled by the motor protein cytoplasmic dynein. The net result of melanosome movement is ultimately forward and they finally reach the tips of dendrites, where they are captured in the actin-rich periphery. There, a small protein, myosin-5a, mediates melanosome binding to actin through two linker proteins Rab27a and melanophilin (reviewed in Park and Yaar, 2012).

In this issue of the Journal of Investigative Dermatology, two articles enhance our understanding of cutaneous pigmentation and how it is affected in melasma. Dynooldt et al. (2012) address the question of which miRNAs are involved in melanogenesis. By using an immortalized cell line of mouse melanocytes, melan-A, the authors observed that solar-simulated irradiation of the cells together with forskolin leads to the upregulation/downregulation of several miRNAs, the most prominent of which is miR-145, whose levels are downregulated 15-fold by this treatment. Indeed, overexpression of miR-145 in melan-A cells results in downregulation of myosin-5a, Rab27a, tyrosinase, and Fscn1 proteins. As expected, miR-145 overexpression interfered with melanosomal migration along the dendrites, and in these cells melanosomes aggregated around the nuclei.

In the second article, Kim et al. (2012) examined WIF-1 and Wnt expression in the skin of patients with melasma and compared it with normal controls. Melasma is a hyperpigmentary disorder affecting many darker-skinned individuals including Hispanics, Asians, and Middle Easterners. It is related to sun exposure and to hormones such as those used in oral contraceptives and those present during pregnancy. The authors observed increased Wnt expression in the skin of melasma patients compared with that of normal controls, as well as decreased WIF-1 expression in keratinocytes in the skin of patients with melasma. Knocking down WIF-1 expression in cultured keratinocytes and/or fibroblasts increased tyrosinase expression in keratinocyte/melanocyte cocultures and enhanced melanosome transfer to keratinocytes. This was reversed by treating the melanocyte monocultures or keratinocyte/melanocyte cocultures with rhWIF-1, suggesting that melasma is causally related to disruption of the Wnt signaling pathway.

The importance of the first study is the identification of a previously unknown molecule miR-145, which appears to be central to the pigmentation process. The second study identifies, at least in part, a mechanism involved in melasma development. These studies provide good examples of how molecular biological techniques may be used to dissect the complex cellular pathways that control pigmentation and to identify specific molecules involved in the pigmentation process. It is possible that these molecules will be future targets manipulating pigmentation. For example, the miRNA effect could be inhibited by small interfering RNA (siRNA). It has been shown in other systems, including in vivo in cardiac disease, that specially designed siRNAs bind miRNA precursors, depleting the miRNAs and neutralizing their effects (Li et al., 2009). Such an approach could be used to target key miRNAs involved in pigmentation through effects on the expression and activity of several downstream genes. The second study reasserts the importance of signals from neighboring keratinocytes and fibroblasts in the control of melanin synthesis and suggests that targeting keratinocytes, cells that are readily accessible to external manipulation, could be used to modulate pigmented processes in the skin.

REFERENCES


