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Patterning Skin Pigmentation via Dickkopf

Howard Y. Chang¹

One of the striking regional variations in skin is its pigmentation. Yamaguchi *et al.* further dissect the mechanism of regional pigmentation by assessing the effects of dickkopf 1 (DKK1), an antagonist of the Wnt pathway produced in lightly pigmented skin, on melanocyte gene expression. The results provide a plethora of candidate genes that may mediate DKK1's inhibitory effects on melanocyte function.

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The pigmentation of skin and hair is patterned across the body in many animal species, including humans. The regional and anatomic patterns of pigmentation are important for mate selection and camouflage. Indeed, many characteristic patterns of pigmentation are recognized in the animal kingdom and have been the subject of genetic investigation in the laboratory, such as mutants in mouse coat color. Anatomic variation in skin or hair pigmentation can arise because of alterations in melanocyte migration, melanocyte proliferation, and melanosome transfer (Bennett and Lamoreux, 2003). Although many basic mechanisms of melanocyte biology and function have been successfully elucidated, less is understood regarding how these processes are controlled to achieve spatial patterns of variation in the body.

A classic example of regional variation in coat color is the hypopigmentation of mouse coat hair on the ventral body surface. In mice, the dorsal (back) pigmentation is black and transitions to yellow and cream colors on the ventrum (belly). This is due to ventral-specific synthesis in dermal papilla cells of an isoform of agouti, a short-ranged extracellular signaling protein that causes melanocytes in the nearby hair follicle to switch from synthesis of black eumelanin to red/yellow

pheomelanin (Millar *et al.*, 1995). The ventral-specific induction of agouti is controlled in part by Tbx15, a T-box transcription factor that is expressed in dorsal mesenchyme and represses agouti expression (Candille *et al.*, 2004). Interestingly, Tbx15 is required for both the hypopigmentation and the shorter length of ventral hairs, demonstrating coordinate control of epidermal and melanocytic fates by a regional mesenchymal signal (Candille *et al.*, 2004).

The authors explore the mechanisms by which non-hair-bearing palmoplantar skin becomes hypopigmented.

Yamaguchi *et al.* (2007, this issue) explore the mechanisms by which non-hair-bearing palmoplantar skin becomes hypopigmented. Palmoplantar skin contains five times fewer melanocytes than trunk skin (Yamaguchi *et al.*, 2007). Using microarray analysis, Yamaguchi, Hearing, and colleagues previously identified dickkopf 1 (DKK1), a secreted antagonist of the Wnt pathway, which is relatively induced in palmoplantar fibroblasts as compared with trunk-

derived fibroblasts (Yamaguchi *et al.*, 2005). Addition of DKK1 to melanocytes *in vitro* inhibited their proliferation and melanin-synthetic activity and repressed expression of microphthalmia-associated transcription factor (MITF), the master transcription factor of melanocyte fate. Millar and colleagues previously showed that uniformly enforced expression of DKK1 via the keratin 14–DKK1 transgene blocks hair follicle development and causes skin hypopigmentation, consistent with the idea that high DKK1 levels might account for the regional features of palmoplantar skin (Andl *et al.*, 2002).

Yamaguchi and colleagues (2007) have now characterized the functional effects of DKK1 stimulation of melanocytes on Wnt signaling and genome-wide transcriptional program. The authors show that DKK1 protein is induced in palmoplantar skin as compared with trunk skin, and that palmoplantar melanocytes are characterized by alterations of the Wnt signaling pathway *in situ*, decreased β -catenin, and decreased glycogen-synthase kinase 3 β (GSK3 β) level, but increased phosphorylation on serine 9 of GSK3 β (the two latter findings are expected to decrease GSK3 β activity). Exposure of melanocytes in culture or in three-dimensional reconstituted skin equivalents to recombinant human DKK1 recapitulated these features of palmoplantar skin. The authors further performed microarray analysis to identify a plethora of genes that are altered in expression in melanocytes as a consequence of DKK1 exposure. Some enticing candidate genes include those functioning in apoptosis (*CADD45B*, *TNFRSF10A*), melanocyte function (*MITF*, *HPS4*, *SV2B*, *STX5A*, *MLPH*), and feedback among Wnt signaling (*KRN1*, *LRP6*, *WNT5A*, *WISP1*).

The findings of Yamaguchi *et al.* (2007) raise many questions. First, which of these candidate genes functionally mediate DKK1's inhibitory effects on melanocyte function? Second, since DKK1 inhibits MITF expression, which of the numerous alterations in gene expression are mediated directly via inhibition of Wnt

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signaling, and which are mediated via inhibition of MITF? Because GSK3 β inhibits β -catenin function in canonical Wnt signaling by causing β -catenin degradation, the putative inhibition of GSK3 β activity (via serine 9 phosphorylation and lower protein level) in the context of DKK1 exposure and Wnt pathway inhibition is paradoxical. GSK3 β can directly phosphorylate and activate MITF (Takeda *et al.*, 2000), and inhibition of GSK3 β may inhibit MITF independently of β -catenin. Third, is DKK1 the only or main signal that mediates the unfavorable melanocytic environment in palmoplantar skin? Fourth, and most fundamental, how is the regional expression of DKK1 in fibroblasts controlled?

In summary, the data of Yamaguchi *et al.* (2007) add to the evidence that regional variation of skin is patterned by reciprocal epithelial–mesenchymal interactions. Fibroblasts from different anatomic sites are systematically differentiated according to their position along three developmental axes and retain key features of the embryonic positional memory in the form of site-specific Hox gene expression (Chang *et al.*, 2002; Rinn *et al.*, 2006). Palmoplantar fibroblasts are able to reprogram trunk keratinocytes in coculture to induce palmoplantar keratin and, via elaboration of DKK1, help induce hypopigmentation of palmoplantar skin (Yamaguchi *et al.*, 1999; Yamaguchi *et al.*, 2007). A better understanding of these molecular mechanisms should shed light on the etiologies of melanocytic diseases, such as vitiligo and acral lentiginous melanoma, which demonstrate unique anatomic predilection and natural histories.

CONFLICT OF INTEREST

The author states no conflict of interest.

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The Dumb ErbB Receptor Helps Healing

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ErbB3 receptor is a member of the epidermal growth factor (EGF) receptor (ErbB1) family. Okwueze *et al.* have transfected this receptor in a pig model of wounds and demonstrate that it accelerates the resurfacing of the wounds when combined with epiregulin or heparin-binding EGF. Currently, only hypotheses can be proposed to explain the observations.

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The cellular environment has a crucial influence on the normal physiology of skin cells, dermal and epidermal. Indeed, cell behavior is under the control of interactions with the extracellular matrix and with neighboring cell partners, but it is also under the control of bathing growth factors and cytokines. After cutaneous wounding, the surviving cells present in the vicinity of the injured tissue must receive triggering information in order to initiate and maintain a proper physiology during the tissue reconstruction. The dermal response and the epidermal reaction have complementary though very different goals during healing. While der-

mal cells have to elaborate the granulation tissue, epidermal cells are committed to resurface the wound in order to repair the epidermal barrier.

Growth factors are involved at several levels during wound healing, and their addition in pharmacological amounts benefits the initiation and maintenance of neoangiogenesis, extracellular matrix secretion, and cell migration and proliferation (for a comprehensive review, see Werner and Grose, 2003). In order to re-epithelialize the wound by keratinocyte migration and proliferation, growth factors such as the epidermal growth factor (EGF) and relatives have demonstrated some efficacy (Werner

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