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A New View of Vitiligo: Looking at Normal-Appearing Skin

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Debate over the pathogenesis of vitiligo is still ongoing among scientists, with several hypotheses currently under consideration. The study by Wagner *et al.* in this issue focuses on the role of E-cadherin-mediated cell adhesion in vitiliginous epidermis under oxidative and mechanical stress. Their work highlights how alterations in cell–cell adhesion across nonlesional melanocyte membranes in patients with vitiligo argue for primary intrinsic defects in the melanocytes.

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Vitiligo, the most common disorder of depigmentation, is an acquired disease characterized by a progressive loss of melanocytes from the epidermis and follicular reservoir. New definition, assessment, and treatment criteria have been proposed for clinical research in vitiligo (Ezzedine *et al.,* 2012; Eleftheriadou *et al.,* 2015).

Despite recent studies that have contributed new *knowledge* about the disease, understanding its pathogenesis remains a major challenge. Although several hypotheses have been proposed, an autoimmune response against melanocytes remains the leading candidate. Accordingly, genetic defects in loci encoding immunoregulatory proteins and melanocyte components that mediate the immune targeting of melanocytes have been reported (Jin *et al.*, 2012). Nevertheless, recent evidence argues for intrinsic metabolic defects in nonlesional melanocytes, leading to intracellular oxidative stress, as the primary intracellular signal for melanocyte degeneration. Recognizing that living cells are subjected to exogenously or endogenously produced reactive oxygen species, elevated oxidative stress may be the initial event that leads to the activation of the antimelanocyte immune responses in patients with genetic predisposition to autoimmunity (Dell'Anna and Picardo, 2006; Schallreuter *et al.*, 2012; Denat *et al.*, 2014; Ezzedine *et al.*, 2015). Consistent with the idea that increased oxidative stress and an impaired ability to manage stress effectively are hallmarks of vitiligo, is the observation that melanocytes from nonlesional skin show alterations of pathways leading to a stress-induced premature senescence-like phenotype (Bellei *et al.*, 2013).

Nevertheless, the mechanisms of melanocyte disappearance remain uncertain. Harris *et al.* (2012) demonstrated that depigmentation is accompanied by an accumulation of autoreactive CD8+ cells and local INF-γ production in the skin, supporting an autoimmune hypothesis. Still, plasmacytoid dendritic cells, which are part of the perilesional cellular infiltrate and the major IFN-α-producing cell subset, may sustain the recruitment and activation of T cells (Bertolotti *et al.*, 2014). In support of this mechanism, apoptosis in vitiligo melanocytes has also been demonstrated (Wu *et al.*, 2013).

The paper by Wagner *et al.* (this issue, 2015) provides new insight into the loss of melanocytes by demonstrating altered cell–cell adhesion that, in turn, is linked to the absence and discontinuous distributions of E-cadherin in normal-appearing skin. E-cadherin is one member of a family of Ca^{2+}-dependent transmembrane proteins, and it mediates melanocyte–keratinocyte interactions in the epidermis. In vitiligo, its loss from the membrane specifically affects melanocytes, because usual levels are much lower than in keratinocytes. Moreover, B-catenin, the partner of E-cadherin in regulating cell–cell adhesion, is similarly absent or discontinuously distributed in melanocyte membranes from nonlesional skin of patients with vitiligo. Melanocyte distribution in the basal layer of nonlesional skin is altered. Although the total number of melanocytes is similar to that of controls, in vitiligo more melanocytes are detached from the basal membrane and located in a suprabasal location where they seem to be more susceptible to apoptosis. Interestingly, IL-1β expression is similar to that of control skin, suggesting that alterations in cellular adhesion cannot be attributed to previous activation of an inflammatory process.

These data are in agreement with the melanocytorrhagy hypothesis that has been proposed as the primary event in melanocytic detachment following a mechanical trauma (Gauthier *et al.*, 2003) and with the reduced number of melanocytes in the basal layer of reconstructed skin using melanocytes from subjects without vitiligo (Cario-André *et al.*, 2007).

However, in mice with E-cadherin-deficient melanocytes, depigmentation occurs only after mechanical stress that is caused by repeated brushing of tail skin and in a model of reconstructed epidermis with normal melanocytes after exposure to H_2O_2 that leads to E-cadherin destabilization. In skin biopsies from patients with vitiligo, E-cadherin alterations are associated with lipoperoxidative damage. Therefore, persistent and widespread stress affecting the distribution of E-cadherin across melanocyte membranes in patients with vitiligo, before the appearance of clinical lesions, cause functional impairment, arguing for primary defects in the melanocytes. *In vivo* confocal microscopy in nonlesional skin of patients with vitiligo have shown abnormal distribution patterns of brightness at the dermoepidermal junction, suggesting that changes in light reflectance indexes correlate with incomplete distributions of pigment at the basal cell level (Ardigo *et al.*, 2007).

Dissociation of melanocytes from the basal membrane may be regulated by growth factors and cytokines released by epidermal and dermal cells. In melanoma cells, hepatocyte growth factor and ET-1 downmodulate E-cadherin expression, allowing melanocytes to dissociate from keratinocytes and to migrate through intercellular spaces (Haass and Herlyn, 2005).

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Clinical Implications

- In vitiligo, all the skin is affected.
- Modification of pigment distributions in the skin may be associated with other alterations, such as defects in the epidermal barrier.
- Stabilization of the disease, by targeting nonlesional skin, is an additional challenge for improving the benefits of treatment.
- Full-body phototherapy may stabilize the disease by inducing the differentiation of melanocytes, with consequent improvements in cell–cell adhesion.
- Counteracting extracellular and intracellular oxidative stress may contribute to reducing melanocyte detachment and disease progression.

Recently, immunohistochemical examination of E-cadherin in tissue samples collected from patients with vitiligo, after punch grafting, revealed that melanocytes from normally pigmented donor sites may migrate toward lesional skin and repopulate the depigmented areas because of decreased E-cadherin expression (Kovacs *et al.*, 2015). The mechanisms that underly the activation of melanocytes after punch grafting have not been fully explained. Nevertheless, the process might be regulated by epidermal and dermal cells that should be able to manage cell adhesion actively.

Therapeutic options for vitiligo are still limited. Although some mechanisms underlying the interplay between oxidative stress and immunity have been postulated (Richmond *et al.*, 2013), understanding mechanisms that cause oxidative stress could provide valuable information to identify new therapeutic targets. The challenge will be to maintain cells metabolically active as requirement for sustaining the energy demand and coping with oxidative stress. Moreover, the analysis has to be extended to pigmented skin to both identify early events in "silent" vitiligo melanocytes and prevent the spread of the disease.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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EDA Fibronectin in Keloids Create a Vicious Cycle of Fibrotic Tumor Formation

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During the early phase of wound healing, first plasma fibronectin (FN) and then *in situ* FN are deposited at the site of injury. *In situ* FN—FN made by tissue cells at the injury site—often contains an extra domain A (EDA) insert. Multiple wound-related signal transduction pathways control the deposition of EDA FN, and the EDA insert can in turn trigger pathways that induce inflammation, increased extracellular matrix molecule deposition including FN and collagen, and activation of fibroblasts. Together these pathways can create a vicious cycle that leads to fibrosis or keloid formation.

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