Repigmentation through Melanocyte Regeneration in Vitiligo

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KEYWORDS

• Vitiligo • Repigmentation • Melanocyte stem cell • Bulge • Hair follicle • Proliferation • Migration • Differentiation

KEY POINTS

- Repigmentation is an active process during epidermal crisis reversing the loss of epidermal melanocytes.
- It usually develops in hair-bearing areas.
- The most common clinical presentation is the perifollicular pattern.
- The initiating event is the activation of melanocyte precursors from the hair follicle and of immature melanocytes from the basal epidermis.
- It is induced by different stimuli: UV light, drugs (steroids, calcineurin inhibitors).

INTRODUCTION

The loss of epidermal mature melanocytes in vitiligo depends on melanocyte-specific CD8+ cytotoxic T lymphocytes. It is reversed by halting the immune attack and by activating melanocyte precursors in the bulge and hair follicle infundibulum, to proliferate, migrate, and differentiate through the process called repigmentation.[1–4] Although repigmentation refers to the replenishment of pigment cells only, keratinocytes in vitiligo skin demonstrate architectural abnormalities and are also likely to be directly involved in repigmentation. Changes of the keratinocytes architecture seem to appear in the absence of basal melanocytes, in the sun-exposed skin. Therefore, significant increase in thickness of both stratum corneum and viable epidermis in vitiligo-depigmented skin, as compared with the adjacent, normal-appearing skin, was reported.[5] This increase likely occurs as an adaptive response to lack of melanin that can minimize and counteract the harmful UV effects on the skin.

Based on current knowledge, vitiligo repigmentation depends on available melanocytes from 2 sources:

- The hair follicle, which is the main source of pigment cells and is often unaffected by the T cell–mediated attack, likely because the hair follicle bulge is an immune privileged location[6]
- The epidermis at the lesional borders, which contains a pool of functional melanocytes and represents a secondary source for repigmentation

Melanocyte activation, followed by migration, proliferation, and differentiation is triggered by several stimuli, such as UV radiation (delivered as treatment or by natural sunlight) and drugs

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(systemic and topical steroids and topical calcineurin inhibitors).

CLINICAL PATTERNS OF REPIGMENTATION AND THE REPIGMENTATION SOURCES

There are 4 classic repigmentation patterns observed on clinical examination[7–9]: perifollicular (most common) (**Fig. 1**A-i), marginal (see **Fig. 1**A-ii),[9] diffuse (see **Fig. 1**A-iv),[7] and combined, which includes more than one pattern (an example of marginal combined with perifollicular pattern is provided in **Fig. 1**A-v).[9] A fifth newly described repigmentation pattern, the medium-spotted patern,[10] is presented in **Fig. 1**A-vi.[11]

The perifollicular pattern presents as small, round, pigmented macules around the hair follicles (see **Fig. 1**A-i). This clinical observation was confirmed by numerous previous *in vivo* studies[12–16] that identified amelanotic, inactive, 3,4-dihydroxy-L-phenylalanine (DOPA)(−) melanocytes in the infundibulum outer root sheath of hair follicles collected from healthy individuals[12,13,16,17] or from vitiligo patients.[14,15,18] The origin of DOPA(−) melanocytes was later identified as the hair follicle bulge (both in the transgenic mouse model[19] and then in human skin).[20] From this location melanocyte precursors ascend to repopulate the depigmented epidermis (**Fig. 1**B, right side) in the ultraviolet radiation (UVR)-treated vitiligo. Activation by UV treatment or ionizing radiation induces these precursors to migrate, proliferate, and differentiate, finally expressing the full pigmentation pathway in the interfollicular

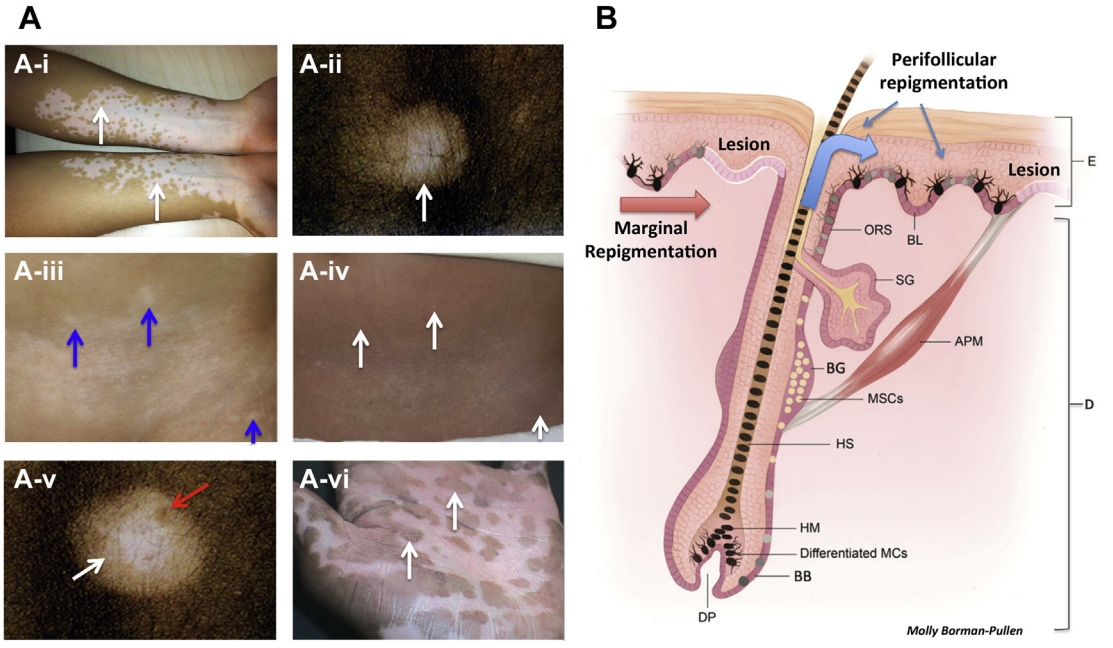

Fig. 1. (*A*) Clinical patterns of repigmentation. (*A-i*) Perifollicular pattern-multiple black dots of pigment are seen around the hair follicles (*white arrows*) in a patient with vitiligo treated with narrow band UVB (NBUVB). (*A-ii*) Marginal repigmentation pattern presented as a pigmented rim at the borders of the lesions (*white arrow*). (*A-iii*) Depigmented spots (*blue arrows*) treated 12 weeks with NBUVB repigment the skin following a diffuse repigmentation pattern, as indicated in (*A-iv*) by white arrows. (*A-v*) Combined repigmentation pattern including marginal pattern (*white arrow*) and perifollicular pattern (*red arrow*). (*A-vi*) Medium-spotted repigmentation pattern[10] in a patient who underwent psoralen plus UVA treatment. Repigmentation of palmar surface presents as round brown macules (*white arrows*). (*B*) Cellular mechanism of perifollicular repigmentation (*right side, blue arrows*) and marginal repigmentation (*left side, red arrow*) in human vitiligo. APM, arrector pili muscle; BB, bulb; BG, bulge; BL, basal layer; D, dermis; DP, dermal papilla; E, epidermis; HM, hair matrix; HS, hair shaft; MCs, melanocytes; MSCs, melanocyte stem cells; ORS, outer root sheath; SG, sebaceous gland. ([*A-i, ii, v*] *From* Gan EY, Gahat T, Cario-André M, et al. Clinical repigmentation patterns in paediatric vitiligo. Br J Dermatol 2016;175:555–60, with permission; and [*A-iii, iv*] Yang YS, Cho HR, Ryou JH, et al. Clinical study of repigmentation patterns with either narrow-band ultraviolet B (NBUVB) or 308 nm excimer laser treatment in Korean vitiligo patients. Int J Dermatol 2010;49(3):317–23, with permission; and [*A-vi*] Davids LM, du Toit E, Kidson SH, et al. A rare repigmentation pattern in a vitiligo patient: a clue to an epidermal stem-cell reservoir of melanocytes? Clin Exp Dermatol 2009;34(2):246–8, with permission; and [*B*] This cartoon was drawn by Molly Borman-Pullen, biomedical illustrator, Fort Collins, CO.)