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Bone Marrow-Derived Cells Contribute to Epithelial Engraftment during Wound Healing

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Recent findings suggest that bone marrow-derived cells (BMDC) may contribute to tissue maintenance throughout the body. However, it is not yet known whether marrow-derived epithelial cells are capable of undergoing proliferation. Our laboratory has shown that BMDC engraft as keratinocytes in the skin at low levels (≤ 1%) in the absence of injury. Here we show that skin damage affects the degree of engraftment of BMDC as keratinocytes and that the keratinocytes are actively cycling. Female mice reconstituted with sex-mismatched BM were wounded by punch biopsy and incision. At the wound site, engraftment of BMDC as epidermal cells increased within 1 day, and continued to increase to approximately 4% by 3 weeks after injury. Using a Cre-lox system, fusion of BMDC with epithelial cells was ruled out. BMDC-derived epithelial cells at the wound edges expressed Ki67, a marker for actively cycling cells, and this proliferation correlated with an increase in the number of donor-derived cells within the wound. Donor-derived cytokeratin 5-expressing cells were rare, suggesting that BMDC do not engraft as epidermal stem cells, and the level of engraftment peaked and then decreased over time, further suggesting that BMDC may assist in early wound healing by engrafting as transit-amplifying cells, which then differentiate into keratinocytes. ***(Am J Pathol 2004, 165:1767–1772)***

We have shown that, in the absence of injury, bone marrow-derived cells (BMDC) engraft at low levels as epithelial cells in the liver, lung, GI tract, and skin. It is not yet clear whether this phenomenon is due to transdifferentiation of a hematopoietic stem cell, or whether the marrow contains pluripotent pre-hematopoietic cells that have not yet initiated a gene expression pattern that commits them to either a hematopoietic or an epithelial fate (reviewed in[1]).

According to recent studies, BMDC show an increased contribution to tissues under pathological conditions. Following acute myocardial infarction, BMDC engraft as multiple cell types that promote survival/regeneration of heart tissue.[2,3] A more pronounced effect is seen in a mouse model of tyrosinemia, where fusion of BMDC with diseased cells results in the formation of functional hepatocytes and restores liver function.[4] These findings led us to investigate whether cutaneous injury leads to increased engraftment of BMDC as epidermal cells.

To allow for tracking of the BMDC, we reconstituted lethally irradiated mice with sex-mismatched BM. Following engraftment, we wounded the skin with full-thickness punch biopsies and incisional wounds, each of which heals by secondary intention. Analysis of the healing skin at different times showed that engraftment of BMDC as epidermal cells in the wounded area was significantly greater than in unwounded skin over the same time interval. The marrow-derived epithelial cells just beyond the wound edges were undergoing proliferation. Fusion was ruled out using the loxP-Cre system. Based on the pattern of engraftment over time, a conceptual model of this engraftment is proposed.

Materials and Methods

Bone Marrow Transplantation and Skin Damage

Female B6D2F1 mice were transplanted with 1×10^6 male whole bone marrow cells after lethal irradiation with

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1200 cGy as previously described.[5] After 21 days, the bone marrow recipients were anesthetized with ketamine and xylazine and underwent a full-thickness skin punch biopsy and linear wound with a scalpel blade in separate locations. At five time points thereafter, on days 1, 3, 5, 14, and 21, four recipient animals were sacrificed and normal undamaged skin as well as the two wounded areas were harvested for histology and Y-chromosome analysis by fluorescence *in situ* hybridization (FISH). Specimens of bone marrow and spleen were also obtained for analysis. In a similar fashion, five control animals underwent irradiation and transplantation, but no wounding. In addition, five male control animals that were neither irradiated nor transplanted were wounded to provide Y-chromosome controls for each time point. One of each control group was sacrificed at days 1, 3, 5, 14, and 21 and had skin, bone marrow, and spleen removed for analysis.

A loxP-Cre recombinase system was used to examine whether fusion occurs between BMDC and host cells as described previously.[6] Briefly, BM was obtained from Z/EG mice[7] (a kind gift of Dr. Corrinne Lobe, Ontario, CA), in which the transgene cassette consists of the chicken β-actin promoter driving expression of a β-galactosidase/neomycin-STOP reporter gene. This is flanked by two loxP sites and followed downstream by EGFP. Expression of β-galactosidase only is driven by the β-actin promoter until Cre-mediated recombination occurs, at which point the β-galactosidase-STOP DNA is excised and the downstream EGFP is expressed instead. BMT recipients were transgenic female mice that ubiquitously express Cre recombinase[8](Jackson Laboratories, Bar Harbor, ME). These animals were wounded 3 to 6 weeks after BMT, and then were sacrificed 7, 14, and 21 days after wounding.

All tissues were fixed in formalin and paraffin-embedded. Skin epithelial cells were visualized by immunohistochemistry for cytokeratins using DAB, photographed, and then stained by FISH for the Y chromosome as previously described.[9] Analysis was performed by counting all of the Y chromosome-positive cytokeratin (diaminobenzidine)-positive cells in a given field versus those that were not Y chromosome-positive. Because 3-μm sections cut through the nucleus, the Y chromosome is not always apparent in male-derived cells. Therefore, the percentage of Y chromosome-positive keratinocytes in male controls was set to 100% and data derived from the transplanted animals were corrected for this Y-chromosome sampling by normalization to the male control.

Ki67 Analysis

To determine the proliferation profile of both BM-derived and endogenous skin cells, FISH and immunofluorescence were used to co-visualize the Y-chromosome, cytokeratin, and the marker of actively cycling Ki67 cells.[10] Slides were deparaffinized, and hydrated with an ethanol series (100%, 95%, 70%, 50%). Antigen retrieval for the Ki67 antigen was performed using citrate buffer (pH 6.0) at 95°C for 20 minutes. After incubation with the anti-Ki67 primary antibody, FISH was performed. This order was used because the acidic citrate buffer can destroy the fluorescent FISH signal, and the harsh treatment steps used in the FISH protocol destroy IF antibody signals. For FISH, slides were incubated in 0.2 normal HCl for 20 minutes, washed with water and 2X sodium chloride sodium citrate buffer (SSC), and incubated in 1 mol/L sodium thiocyanate (NaSCN) for 30 minutes at 80°C. Slides were washed, dehydrated in a graded ethanol series, and air dried. Digoxigenin-labeled murine Y chromosome was added, then slides heated to 95°C for 5 minutes, 22°C for 1 minute, 95°C for 5 minutes, and then placed at 37°C overnight. Then the Y chromosomes were stained with rhodamine-labeled anti-digoxigenin antibody as previously described.[9]

For staining with Ki67 and anti-cytokeratin, endogenous biotin was blocked (Vector Labs biotin blocking kit), then 1% bovine serum albumin (BSA) in 1X TBS was then added for 20 minutes at room temperature. Next, slides were incubated for 35 minutes at room temperature with rat anti-mouse Ki67 antibody (clone TEC-3, Dako), washed and incubated for 1 hour with biotinylated goat anti-rat IgG. After washing, rabbit anti-mouse wide-spectrum cytokeratin antibody (Dako, Carpinteria, CA) was administered for 35 minutes at 37°C, washed, and Cy5-labeled goat anti-rabbit IgG (Molecular Probes, Eugene, OR) added for 1 hour at room temperature. After incubation with FITC-labeled streptavidin, slides were washed and allowed to air dry completely. DAPI-containing Vectashield (Vector Labs, Burlingame, CA) was then added to the slides under coverslips, and the slides were visualized under an Olympus fluorescence microscope. Statistical analyses were performed using a one-tailed *t*-test.

Results

Skin Wounds Healed by Secondary Intention

Both the full-thickness linear wound and the punch biopsy healed by secondary intention due to the lack of apposed edges, and similar pathological findings were found in response to both wound types. Hematoxylin and eosin-stained samples of the punch biopsy wounds at day 1 exhibited ulceration, extending into the superficial subcutis, lined by fibrin and neutrophils. There was secondary fibrinoid degeneration of blood vessels beneath the ulcer. The deep panniculus exhibited a mild diffuse infiltrate, predominantly of neutrophils, associated with abundant extravasated erythrocytes. Samples from day 3 (Figure 1A) showed the ulcer defect filled by crust, comprised of serum and neutrophils, beneath which was organized fibrin. Toward the base of the lesion were lymphocytes, histiocytes, and occasional eosinophils and neutrophils, associated with plump fibrohistiocytes. The epidermis adjacent to the ulcer exhibited acanthosis and reactive enlargement of keratinocytes, with prominent mitotic figures, most evident in adjacent superficial hair follicle epithelium. Samples from day 5 (Figure 1B) exhibited greater organization of fibrin at the surface of the ulcer, diminished crust, and growth of epidermis over

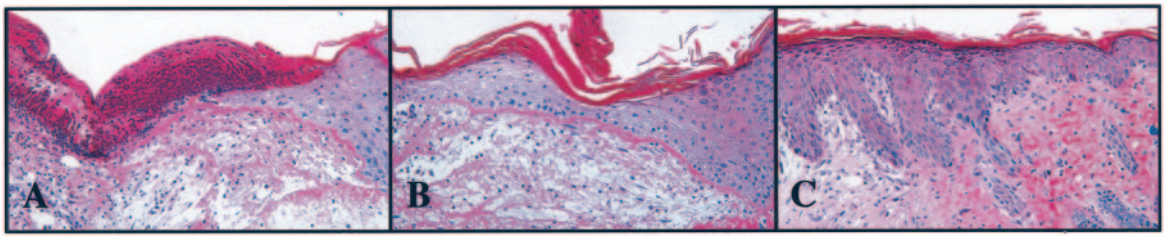

Figure 1. A: Sample from day 3 showing an ulcer defect (**left**) filled by crust, with a mixed underlying inflammatory infiltrate. The epidermis adjacent to the ulcer exhibits acanthosis and reactive enlargement of keratinocytes. **B:** Sample from day 5 exhibiting greater organization of fibrin at the surface of the ulcer, diminished crust, and growth of epidermis over the edge of the ulcer. **C:** Sample from day 14 showing complete re-epithelialization. The epidermis over the scar (**right**) exhibits acanthosis, hypergranulosis, and hyperkeratosis. Fibrin has been replaced by horizontally oriented collagen bundles, interspersed by plump fibroblasts.

the edges of the ulcer. Prominent spindled fibroblasts were present at the ulcer base, associated with an infiltrate, primarily composed of histiocytes. Examination of the slit wounds exhibited similar findings, but showed complete re-epithelialization on day 5. On day 14 (Figure 1C), all samples showed complete re-epithelialization. The epidermis exhibited acanthosis, hypergranulosis, and hyperkeratosis. Fibrin had been replaced by horizontally oriented collagen bundles, interspersed by plump fibroblasts. An increase in capillaries was noted, with predominant vertical orientation. The underlying histiocytic infiltrate was diminished. All samples from day 21 were similar to those of day 14, but exhibited a contracted scar, further diminished inflammatory infiltrate, and fewer capillaries.

BMDC Engraft as Keratinocytes in the Skin

Simultaneous analysis by FISH and immunohistochemistry on single 3-μm paraffin sections was used to definitively identify Y+ cytokeratin-positive cells. Epithelial and hematopoietic cells were distinguished by immunohistochemistry for cytokeratins and a combination of S100 (for histiocytic and dendritic cells), CD45 (common leukocyte antigen), and Mac1 (CD11b). Immunohistochemistry for cytokeratin using DAB precipitation can be visualized both by light microscopy as a brown precipitate and by fluorescence microscopy in the Cy5 channel. Shown in Figure 2 are representative data from damaged skin 5 and 21 days after wounding. The left panels are light microscopic images showing immunohistochemical staining for cytokeratin and the right are fluorescence microscopic images of the same fields after Y chromosome FISH. The white arrows indicate examples of Y+ cytokeratin-positive cells and the green arrows indicate Y+ cytokeratin-negative cells, which likely represent hematopoietic, endothelial, and other non-epithelial cells. For each time point, skin samples from the healing slit wounds, punch wounds, and from uninjured areas were analyzed for each of four mice. For each of the skin samples, at least 200 cytokeratin-positive CD45-cells were counted and assessed for the Y chromosome. The mean ± SD for each time point were normalized to the percentage of cytokeratin-positive cells that were Y+ in male control samples (65 ± 3%, data not shown). In the absence of wounding, the number of BM-derived keratinocytes ranged from 0 to 0.79% with 16 or 24 samples showing no Y+ keratinocytes. At every time point analyzed after injury, there was a statistically significant ($P \leq 0.01$) increase in the percentage of Y+ cytokeratin-positive cells in the healing cut and punch wounds compared to uninjured skin (Figure 3). There was essentially no difference in the number and distribution of donor-derived keratinocytes between the two wound types.

BMDC Rarely Engraft as Cytokeratin 5-Expressing Basal Cells

To address the question of whether BMDC engraft as skin stem cells, which express both cytokeratins 5 and 19, we assessed whether BMDC could engraft as cytokeratin 5+ cells. Staining of the skin samples before and after wounding for co-expression of cytokeratin 5 and Y chromosome revealed only very rare (<0.1%), donor-derived CK5+ keratinocytes. It is unlikely that these rare cells

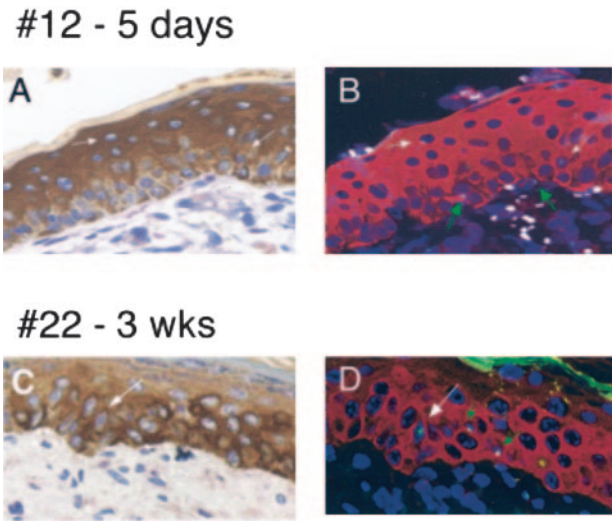

Figure 2. Shown are representative images from two different mice, 5 days (**top**) and 3 weeks (**bottom**) after wounding. Images were taken of the same slide after immunohistochemical staining for cytokeratin (**left**) and Y-chromosome FISH (**right**). After development of the immunohistochemical staining with DAB, the slides were lightly counter-stained with hematoxylin to allow for visualization of nuclei. In the fluorescence panels (**B** and **D**), the red signal derived from the autofluorescence of the DAB in the Cy5 channel, the white signal is from the Y-chromosome FISH, the blue represent DAPI-stained nuclei and the green signal is autofluorescence. The white **arrows** indicate Y+ positive cytokeratin-positive cells. The green **arrows** indicate Y chromosome-positive cells that do not appear to stain for cytokeratin. Original magnification, ×60.

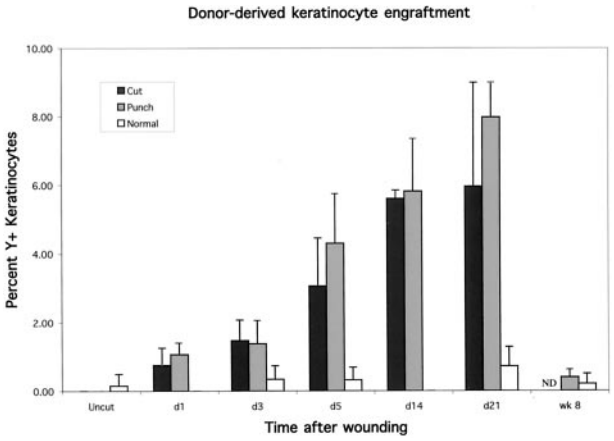

Figure 3. Shown in this graph is the mean ± SD of the percentage of Y chromosome-positive keratinocytes at different times after wounding with either a cut (**black bars**) or punch biopsy (**gray bars**). **Clear bars** indicate the engraftment of marrow-derived keratinocytes in an unwounded area of skin of the same animals that had received wounds at each time point. Note that no Y+ cytokeratin+ cells were found in unwounded skin on d1 or d14. Uncut refers to the control animals that were transplanted but did not receive wounds.

represent skin stem cells because they were not found in the bulge region, where skin stem cells, which express both cytokeratin 5 and cytokeratin 19, are predominantly found. Also, if the BMDC engrafted as skin stem cells, then their progeny would be detectable for many cellular generations. When we assessed skin wounds for engraftment of male BMDC-derived keratinocytes 2 months after punch biopsy (n = 3), only a few rare cytokeratin+ Y chromosome+ cells were detected comprising <1% of the keratinocytes, which further suggests that BMDC do not engraft as long-term self-renewing skin stem cells (Figure 3).

Marrow-Derived Epithelial Cells Proliferate at the Wound Edges

We assessed the proliferation profile of endogenous and BMD epithelial cells to determine whether bone marrow-derived epithelial cells are amplified within the healing skin. Slides were stained for simultaneous analysis of Ki67, a marker of actively cycling cells,[11] cytokeratin, CD45, and the Y chromosome (Figure 4A). We assessed three regions within and around each wound (Figure 4B). We considered the wound itself to be the α region, the edges directly adjacent to the wound to be the β region, and the next more distal region, which was approximately 21 mm from the edge of the wound, to be the γ region. The distribution of actively cycling Ki67+ cells showed an interesting pattern. The first burst of cell divisions occurred 3 days after wounding in the β-region adjacent to the wound, and the second burst occurred 5 days after

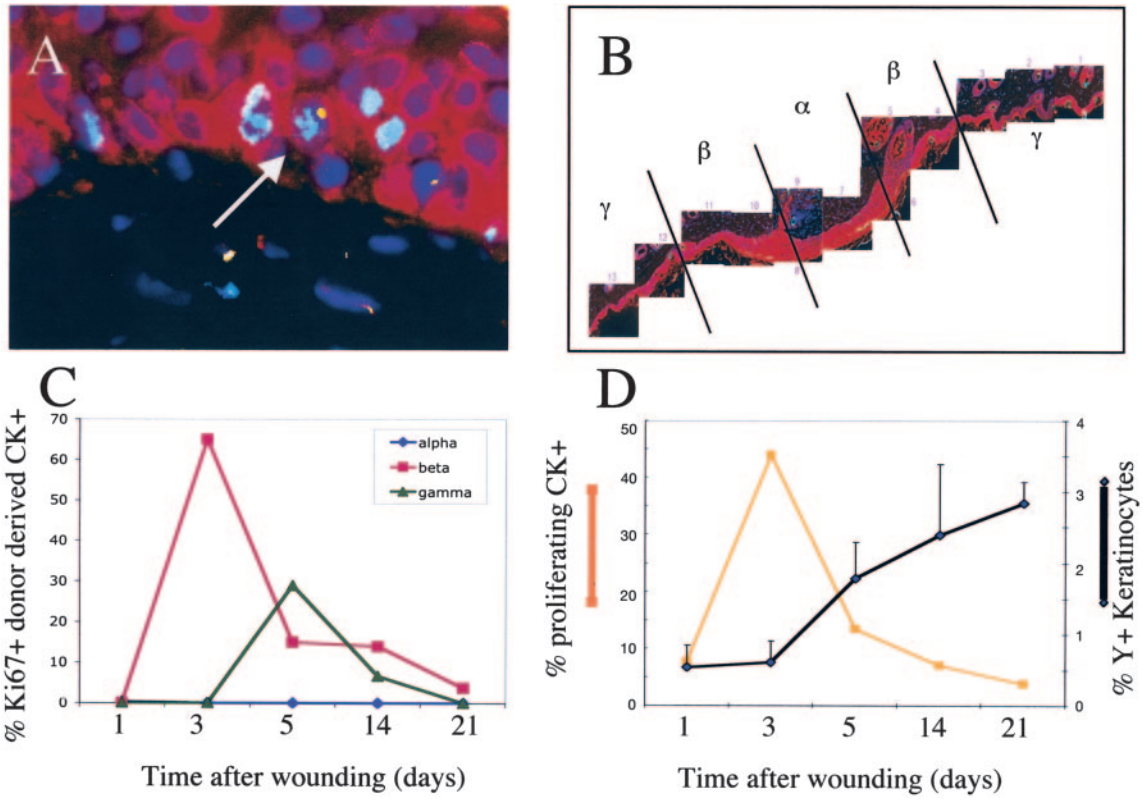

Figure 4. A: Fluorescent staining for Ki67 (light blue nuclei), Y chromosome (yellow), cytokeratin (red), and DAPI for the nuclei (dark blue). The **arrow** indicates Y chromosome+, Ki67+, and cytokeratin+ cells in the basal layer of the skin in the β region 5 days after wounding. **B:** Shown is a composite of a skin wound 21 days after wounding. The α region is the center of the wounded area, and the β region is located at the periphery of the wound. Just outside the highly proliferative β region is the γ α region. **C:** Graph shows the percentage of donor-derived epithelial cells that are Ki67+ in each of the regions delineated in **B** at different times after wounding (α, **circles**; β, **squares**; γ, **triangles**). **D:** Graph shows the percentage of all donor-derived epithelial cells that are proliferating over time (**squares**) on the left axis and the percentage of keratinocytes that are donor-derived (**diamonds**) on the right axis at different times after wounding.

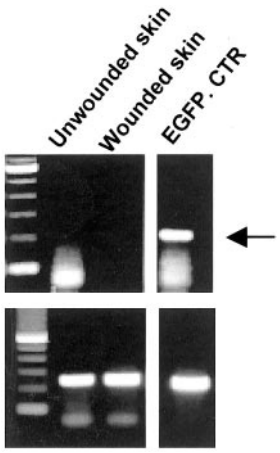

Figure 5. RT-PCR for GFP (**top**) in unwounded and wounded skin as indicated. At **right**, the GFP-positive control is shown. The band present in the lane labeled unwounded skin is significantly smaller than the expected size of the GFP product and represents the primers. β-actin controls are shown on the **bottom**.

wounding in the γ region (Figure 4C). Cycling cytokeratin+ cells were not present within the wound itself (α region, Figure 4C). These data suggest that circulating BMDC come to the wound, and then proliferate before migrating into the wound area proper. When one combines the proliferation data of the β plus the γ regions, there is maximal cell division of BMDC on day 3, which coincides with the steepest increase in the number of BM-derived cytokeratin-positive cells (Figure 4D). Of note, all Ki67 staining was nuclear.

BMDC Do Not Form Epithelial Cells in the Skin by Fusion

We transplanted lethally irradiated female mice that express Cre recombinase in all of their cells with bone marrow from male Z/EG, β-actin-Cre,[8] or Z/EG $\times$ β-actin-Cre F1 (Z $\times$ C F1) donor mice. The Z $\times$ C F1 into Cre transplants serve as a positive control for EGFP expression in donor-derived cells, and the Cre into Cre serve as negative controls. Engraftment of BMDC as keratinocytes in the skin was assessed after inducing full-thickness wounds, which were allowed to heal by secondary intention. After 7, 10, and 21 days, the wounds were excised and examined for BMDC engraftment by simultaneous immunofluorescence for cytokeratin, CD45, and EGFP expression as well as by Y-chromosome FISH. Keratinocytes that stained positively for cytokeratin and the Y chromosome and negatively for CD45 were present in the transplanted, wounded animals, however, no EGFP expression was detected by immunofluorescence (data not shown). In addition, using RT-PCR for EGFP mRNA, which has a sensitivity to detect 1 GFP+ cell in 10^6 total cells,[6] there was no EFGP mRNA in the wounded skin (Figure 5).

Discussion

Epidermal stem cells play a significant role in skin homeostasis and wound repair.[12] First described in a corneal model, these studies were broadened to investigate hair-bearing skin, where the reservoir for the epidermal stem cells is in the follicular bulge of the hair follicle.[13] In response to epidermal damage, these stem cells migrate, proliferate, and differentiate into either matrix epithelial cells, which form the hair shaft, or cornified keratinocytes, which form skin. Here we show that lethally irradiated female mice that have been reconstituted with male bone marrow cells and subsequently wounded express a significant number of Y chromosome-positive epithelial cells in healing wounds. This expression is apparent within days after wounding, and increases over the next 21 days, with the greatest increase seen between days 3 and 5. This increase occurs just after a peak of mitotic activity of the BM-derived epithelial cells immediately adjacent to the wound. A significant correlation between areas known to be undergoing high levels of cell division (β and γ) suggests that BMDC preferentially engraft in highly proliferative regions. BMDC rarely engrafted as cytokeratin 5 basal cells in the follicular epithelium. Based on location and cellular properties, it is most likely that BMDC engraft as transit-amplifying cells and not as skin stem cells.

The pattern of cell division and BM cell engraftment over the time course of wound healing suggests a modified model of wound healing in which cells from the bone marrow invest in wounded epidermis as keratinocytes. We hypothesize that in a wound environment, BMDC are recruited nonspecifically via the inflammatory response. Once in the wound area, the precursor cells are exposed to a microenvironment which normally promotes the migration, proliferation, and differentiation of epidermal stem cells.[14,15] The cells respond to these signals by migrating to and engrafting in zones of active proliferation where they differentiate into transit-amplifying cells. The factors required for recruitment to and differentiation within the damaged skin are not yet known. In related work, Hatch et al[16] showed that, in rats, BMDC may be recruited to the liver in response to SDF1 expression by hepatocytes. In preliminary studies in the mouse, however, no SDF1 expression was detectable by immunohistochemistry in the skin in response to wounding (N.D. Theise and D.S. Krause, unpublished results), and in a human skin wound model, SDF1 levels actually decrease after wounding.[17]

An alternate possibility is that progenitor cells enter the wound area and fuse with the damaged epidermal cells, thereby taking on keratinocyte properties, however, our experiments using a Cre-Lox system failed to detect any fusion with epidermal cells.[6] Thus, these data confirm that adult bone marrow stem cells can differentiate into skin epithelial cells, and suggest a three-tier model for maintenance and repair of the epidermis. The three cell compartments are comprised of fully mature cells, intra-organ stem cells, and circulating, extra-organ stem cells, all contributing to the maintenance of tissue integrity. It is the balance between these three cell compartments that changes with different degrees and perhaps different types of injury. The percentage of engraftment, however, suggests that extra-organ stem cells play, at most, a

minor role in wound repair in the absence of cell mobilizing factors such as G-CSF.

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