Nerve-derived neural crest cells are essential for regeneration in certain animals, such as newts. Here, we asked whether they play a similar role during mammalian tissue repair, focusing on Sox2-positive neural crest precursors in skin. In adult skin, Sox2 was expressed in nerve-terminal-associated neural crest precursor cells (NCPCs) around the hair follicle bulge, and following injury was induced in nerve-derived cells, likely dedifferentiated Schwann cell precursors. At later times postinjury, Sox2-positive cells were scattered throughout the regenerating dermis, and lineage tracing showed that these were all neural-crest-derived NCPCs. These Sox2-positive NCPCs were functionally important, since acute deletion of Sox2 prior to injury caused a decrease of NCPCs in the wound and aberrant skin repair. These data demonstrate that Sox2 regulates skin repair, likely by controlling NCPCs, and raise the possibility that nerve-derived NCPCs may play a general role in mammalian tissue repair.

INTRODUCTION

Insights into potential mechanisms for the regulation of mammalian tissue repair have come from studies of animals that can regenerate limbs, tails, and even the spinal cord, such as amphibians and reptiles. One major conclusion from these studies is that tissue regeneration requires nerve innervation (Kumar and Brockes, 2012). These findings have led to the idea that peripheral nerves may regulate tissue repair in mammals. This possibility has important implications because every tissue in the body is innervated. Indirect support for this intriguing idea comes from recent studies showing that innervation regulates the biology of some adult tissue precursors (Yamazaki et al., 2011; Brownell et al., 2011).

How might nerves regulate tissue repair and regeneration? In newts, neural-crest-derived Schwann cells migrate into the regenerating limb and secrete factors that regulate mesenchymal cell proliferation and regeneration itself (Kumar and Brockes, 2012). In mammals, nerve injury leads to a dramatic dedifferentiation of Schwann cells into a precursor cell state, which is important for appropriate nerve regeneration (Jessen and Mirsky, 2008). Here, we asked whether nerve-derived neural crest precursor cells (NCPCs) play a role in mammalian tissue repair, focusing on adult murine skin. We describe nerve-associated NCPCs in adult skin and show that NCPCs contribute to the regenerating dermis in a Sox2-dependent fashion, and that when Sox2 is ablated, this NCPC response is perturbed concomitantly with aberrant skin repair. Thus, Sox2 regulates skin repair, likely via its actions in Sox2-positive NCPCs, suggesting that nerve-derived NCPCs may play a general role in promoting mammalian tissue repair.

RESULTS

Sox2 Defines Nerve Terminal-Associated NCPCs in Adult Skin

We first defined Sox2-expressing skin populations using mice with EGFP knocked in to the Sox2 allele (Sox2+/EGFP mice; Ellis et al., 2004). Immunostaining of back skin at 8 weeks, when hair follicles are in telogen, showed that Sox2-EGFP was limited to some highly distinctive cells around the hair follicle bulge (Figure 1A) as well as scattered K8-positive Merkel cells (Figure S1A available online), which were previously reported to express Sox2 (Driskell et al., 2011). Here, we asked whether nerve-derived neural crest precursor cells (NCPCs) play a role in mammalian tissue repair, focusing on adult murine skin. We describe nerve-associated NCPCs in adult skin and show that NCPCs contribute to the regenerating dermis in a Sox2-dependent fashion, and that when Sox2 is ablated, this NCPC response is perturbed concomitantly with aberrant skin repair. Thus, Sox2 regulates skin repair, likely via its actions in Sox2-positive NCPCs, suggesting that nerve-derived NCPCs may play a general role in promoting mammalian tissue repair.
we call nerve terminal (NT) cells) were also present in anagen hair follicles at 4 weeks of age, when Sox2-EGFP was also expressed in mesenchymal hair follicle precursors (Figure S1B–S1E), as we previously reported (Biernaskie et al., 2009).

We performed lineage tracing to confirm that NT cells were neural-crest derived, crossing Sox2+/EGFP animals and mice carrying a Wnt1-Cre transgene (which marks neural crest progeny) and a floxed TdTomato reporter gene in the Rosa26 locus. Immunostaining of back skin from 8-week-old Sox2+/EGFP;Wnt1-Cre;R26TdTfl/+ mice showed that TdTomato was expressed in Sox2-EGFP-positive NT cells and in EGFP-negative neural crest cells, including skin nerve cells (Figure 1E) and melanocytes (data not shown). To confirm that NT cells are of neural crest and not dermal origin, we also analyzed Dermo1Cre+/R26YFPfl/+ mice in which Cre recombinase is knocked in to one allele of the Dermo1 transcription factor gene, which is expressed in dermal but not epidermal or neural-crest-derived cells (Yu et al., 2003). In these mice, nestin-positive NT cells did not express YFP (Figure 1F), but almost all dermal cells were yellow fluorescent protein (YFP) positive, including the telogen hair follicle dermal papilla and sheath cells (Figure S1F). Thus, Sox2 defines a unique population of
neural-crest-derived NT cells in hair follicles that persist during all stages of the hair cycle.

**Sox2-Positive NCPCs Contribute to the Regenerating Dermis following Skin Injury**

To ask whether Sox2 was induced in dedifferentiated NCPCs in skin nerves following tissue injury, we performed full-thickness punch wounds on 8-week-old Sox2+/EGFP mice. Immunostaining 5 days postinjury identified many Sox2-EGFP-positive nerve cells that coexpressed p75NTR and S100b (Figures 1G–1I). At 7–9 days postinjury, many Sox2-EGFP-positive cells were also scattered throughout the regenerating dermis (Figure 1J). Virtually all of these coexpressed p75NTR and S100b (Figures 1K and 1L), and many expressed nestin (Figure 1M), consistent with an NCPC phenotype. Some, but not all, of these NCPCs were associated with axons that had sprouted into the healing tissue and expressed the axonal marker PGP9.5 (Figure 1N). Moreover, many were proliferating; when bromodeoxyuridine (BrdU) was administered once a day commencing at the time of injury; ~11% of the Sox2-EGFP-positive cells were BrdU positive by 9 days (Figure 1O).

We definitively established that the Sox2-EGFP-positive cells within the wound were neural-crest derived by performing punch wounds on Sox2+/EGFP; Wnt1-Cre; R26TdTomatofl/+ mice. At 9 days postinjury, virtually all Sox2-EGFP-positive cells within the wound were positive for TdTomato and coexpressed p75NTR and S100b (Figures 2A–2C). These neural-crest-derived cells were still present within the regenerated dermis at 30 days postinjury (Figures 2D–2F).

**Most Sox2-Positive NCPCs within the Regenerating Dermis Are Induced to Express Sox2 Following Injury**

The above data indicate that there are several potential sources of NCPCs within injured skin, including NT cells, which always express Sox2, and cutaneous nerve cells, which are induced to express Sox2 following injury (Merkel cells are not neural-crest derived; Van Keymeulen et al., 2009). To ask which of these potential sources contributed Sox2-expressing NCPCs to the regenerating dermis, we performed lineage tracing with a mouse in which CreERT2 was knocked in to the Sox2 locus (Sox2CreERT2/+ mice; Arnold et al., 2011). We crossed these to R26TdTomatofl/+ mice and exposed them to tamoxifen to induce Cre-mediated recombination of the reporter gene in Sox2-positive cells. We did this either 3 weeks before a punch wound, thereby inducing expression of TdTomato in Sox2-positive NT cells and Merkel cells (Figures 3A and 3B), or at the time of injury, whereby inducing TdTomato in Sox2-expressing cells within the injured nerve (Figures 3C and 3D), in addition...
to NT cells and Merkel cells (Figures 3D–3F). No other cells in the skin were labeled under either condition.

We then compared the number and phenotype of TdTomato-positive cells within the regenerating dermis 9 days postinjury. In mice treated with tamoxifen before the injury, relatively few TdTomato-positive cells were present in the wound bed (Figure 3G). In contrast, in mice treated with tamoxifen at the time of injury, many TdTomato-positive cells were scattered throughout the regenerating dermis (Figure 3H), as seen with the Sox2-EGFP reporter (Figure 1J). In both cases, virtually all of the TdTomato-positive cells expressed p75NTR and S100\(b\) (Figures 3I–3K), consistent with an NCPC phenotype. Thus, some NCPCs within the wound bed originate from NT cells, but most derive from NCPCs that are induced to express Sox2 following injury, likely from cutaneous nerves since other neural crest cells within the skin (such as melanocytes) do not express Sox2 either before or after injury (data not shown). Consistent with this interpretation, when tamoxifen was given at the time of injury, many TdTomato-positive cells appeared to be migrating from local nerves into the wound bed (Figure 3C).

**Acute Deletion of Sox2 in Adult Mice Dysregulates the NCPC Response and Causes Aberrant Skin Repair**

To ask whether Sox2-positive NCPCs were functionally important for skin repair, we conditionally deleted Sox2 in adult mice and asked whether this impaired wound healing. Specifically, we crossed Sox2\(^{fl/fl}\) mice to mice expressing a constitutively expressed CreERT2 in the Rosa26 locus (Sox2\(^{fl/fl}\);R26\(^{CreERT2/+}\) mice; Seibler et al., 2003, Taranova et al., 2006). We injected mice with tamoxifen at 9 months of age, confirmed that this caused recombination of the
floxed Sox2 alleles in the skin (Figure 4A), and performed punch wounds 5 weeks later. Measurement of these punch wounds showed that Sox2 ablation significantly decreased the rate of wound closure over 9 days relative to three different control groups (Figure 4B). Morphological analysis (Figure 4C) confirmed this deficit: Sox2<sup>f/f</sup>; R26<sup>CreERT2/+</sup> mice treated with tamoxifen were significantly impaired with regard to the epithelial gap, wound width, and dermal tissue regeneration relative to controls (Figures 4D–4F). Moreover, the proportion of proliferating, Ki67-positive cells in the regenerating dermis was robustly decreased (Figures 4G and 4H). Deficits in wound healing were also observed in Sox2 heterozygous mice (Figure S2), supporting the conclusion that Sox2 is necessary for skin repair.

Since NCPCs are the only cells within the regenerating skin that express Sox2, these findings suggest that the decreased skin repair is due to a deficit in NCPCs. To test this idea, we quantified the relative proportion of p75NTR-positive NCPCs in the regenerating dermis (Figure 4I). This analysis showed that despite the larger wound area when Sox2 was conditionally ablated (1.62 ± 0.27 mm<sup>2</sup> in Sox2<sup>f/f</sup>; R26<sup>CreERT2/+</sup> mice treated with oil versus 2.57 ± 0.59 mm<sup>2</sup> in Sox2<sup>f/f</sup>; R26<sup>CreERT2/+</sup> mice treated with tamoxifen), the area covered by p75NTR-positive cells and their relative density were both decreased 2- to 3-fold (Figures 4J and 4K). Immunostaining for SOX2 on adjacent sections confirmed that in the Sox2<sup>f/f</sup>; R26<sup>CreERT2/+</sup> mice treated with oil, many cells within the wound bed and adjacent nerves were Sox2 positive, whereas positive cells were not observed in either the wound or nerves in the Sox2<sup>f/f</sup>; R26<sup>CreERT2/+</sup> mice treated with tamoxifen. Thus, Sox2 regulates the NCPC response to tissue injury, and this response is necessary for appropriate skin repair.

**DISCUSSION**

The data presented here support a number of conclusions. First, we identify a population of Sox2-positive neural-crest-derived NT cells around the hair follicle bulge. These cells express an NCPC phenotype and contribute cells to the regenerating dermis following skin injury. Second, we show that skin injury induces expression of Sox2 in skin nerve cells (likely dedifferentiated Schwann cells), and that these cells likely provide the major source of NCPCs in the regenerating dermis. Third, we show that Sox2 is important for this NCPC response, because when Sox2 is genetically ablated, the number of NCPCs within the regenerating dermis is reduced 2- to 3-fold. Finally, we show that an aberrant NCPC injury response, caused by genetic ablation of Sox2, is coincident with significant deficits in skin repair. Thus, Sox2-positive NCPCs contribute to the regenerating dermis. This contribution depends upon normal levels of Sox2, and when this injury response is perturbed, skin repair is aberrant.

One question that arises from this work involves the nature of the NT cells. We show here that these bulge-associated cells are located at nerve terminals, that they resemble NCPCs phenotypically, and that they contribute cells to the regenerating skin. Intriguingly, previous publications have identified NCPC stem cell activity in the hair follicle bulge region (Sieber-Blum and Hu, 2008; Amoh et al., 2005). Moreover, during development, NCPCs migrate into the skin via nerves, where they contribute melanocytes to hair follicles (Adameyko et al., 2009). We therefore propose that NT cells are NCPCs that arrive in the embryonic skin via nerves, are maintained in a precursor state by their hair follicle niche, and function as a reservoir of adult NCPC activity.

A second question involves the origin of the Sox2-positive NCPCs within the regenerating dermis. The Sox2-CreERT2-mediated lineage tracing shows that a large majority of these NCPCs are induced to express Sox2 following skin injury. Because the only neural-crest-derived skin cells that express Sox2 following injury are NT cells and cutaneous nerve cells, it is likely that many of these NCPCs derive from the injured nerve, perhaps from dedifferentiated Schwann cell precursors that express Sox2 (Perrinello et al., 2010; Jessen and Mirskey, 2008). It is, however, formally possible that these Sox2-positive NCPCs originate outside of the skin and are trafficked into the regenerating dermis from a distance, perhaps via the circulation.

Importantly, our findings define a role for NCPCs in promoting skin repair. How then do NCPCs regulate skin repair? Based upon work in amphibians (Kumar and Brockes, 2012), we propose that following injury, nerve-derived, Sox2-positive NCPCs proliferate and migrate together with adjacent mesenchymal cells into injured tissues (e.g., the skin), where they secrete growth factors that regulate mesenchymal cell proliferation and potentially other aspects of wound healing. We also posit that (1) the initial NCPC proliferation and migration are Sox2 dependent (data shown here; Le et al., 2005), and (2) at later repair stages, NCPCs in the injured tissue associate with newly grown axons, differentiate into mature Schwann cells, and once again comprise an essential component of skin nerve innervation. In such a model, nerve-derived NCPCs play two essential roles: they act in a paracrine fashion to enhance tissue repair, and they provide a source of Schwann cells for the newly remodeled innervation. Intriguingly, nerves innervate every tissue in the body, and Schwann cell dedifferentiation is a general response to nerve injury, raising the possibility that nerve-derived NCPCs may play a role in promoting mammalian tissue repair throughout the body.
Figure 4. Genetic Ablation of Sox2 in Adult Mice Causes Aberrant Skin Repair Concomitantly with Deficits in the NCPC Injury Response

(A–K) Sox2^fl/fl^;R26^CreERT2/+^ mice were treated with tamoxifen (Sox2^fl/fl^;Cre+Tam, n = 7) or vehicle (Sox2^fl/fl^;Cre+Oil, n = 6) at 9 months, and punch wounds were performed 5 weeks later. As additional controls, wild-type mice of the same genetic background were treated with tamoxifen (C57/Bl6+Tam, n = 7) or oil (C57/Bl6+Oil, n = 5).

(A) Genomic DNA PCR analysis showing the 297 nt product from the intact floxed allele, and the 589 nt product generated from the floxed allele after Cre-mediated recombination.

(B) Extent of wound closure 3–9 days postinjury. Two-way ANOVA; *p < 0.05 for group effect.

(C) Representative hematoxylin-and-eosin-stained section through the center of the wound bed 9 days postinjury showing the epithelial gap (EG), wound width (WW), and regenerating dermal tissue (RDT).

(D–F) Quantification of the epithelial gap, wound width, and new dermal tissue score.

(G) Ki67+ cells in the wound bed and wound leading edge.

(H) Percent of dermal Ki67+ cells.

(I) p75NTR+ cells in the wound bed.

(J) Quantification of p75NTR+ area.

(K) p75NTR density in the wound bed.

(legend continued on next page)
EXPERIMENTAL PROCEDURES

Animals and Tamoxifen Treatments
This study was approved by the HSC Animal Care Committee in accordance with CCAC guidelines. Sox2CreERT2/+(Ellis et al., 2004), Dermo1Cre+ (Yu et al., 2003), Wnt1-Cre (Danielian et al., 1998), Sox2CreERT2/+ (Arnold et al., 2011), R26TdTomatoRlN (Madsen et al., 2010), R26YFPRlN (Srinivas et al., 2001), Sox2fl/fl (Taranova et al., 2006), and R26CreERT2/+ (Seibler et al., 2003) mice are described in the Supplemental Experimental Procedures. Mice were injected intraperitoneally daily for 5 consecutive days with tamoxifen (3 mg/day) or with sunflower oil. Punch wounds were performed as previously described (Biernaskie et al., 2009; Supplemental Experimental Procedures), and in some experiments, 100 mg/kg BrdU was injected daily commencing on the day of injury.

Tissue Preparation and Immunostaining
We performed morphometric analysis on paraffin-embedded sections and immunofluorescence on cryosections (Biernaskie et al., 2009). Fluorescence images were captured by confocal microscopy. For further details and antibodies, see the Supplemental Experimental Procedures.

Quantitative Analyses and Statistics
Wound closure (calculated as the percentage of healed area relative to the initial wound size) and quantitative morphometric analyses (performed on central sections where wound diameter was largest) are described in the Supplemental Experimental Procedures. The proportion of Ki67-positive cells was measured at the leading edges of the newly formed dermis, and the p75NTR-positive cell area was measured throughout the entire dermal portion of the wound bed. Quantitative analyses were performed blind. Statistics were obtained using Student’s t test (one- or two-tailed as appropriate) or one- or two-way ANOVA as indicated in the text. Error bars indicate SEM.

SUPPLEMENTAL INFORMATION
Supplemental Information includes two figures and Supplemental Experimental Procedures and can be found with this article online at http://dx.doi.org/10.1016/j.stemcr.2013.04.004.

LICENSING INFORMATION
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REFERENCES
Adameyko, I., Lallemand, E., Aquino, J.B., Pereira, J.A., Topilko, P., Müller, T., Fritz, N., Belajeva, A., Mochii, M., Liste, I., et al. (2009). Schwann cell precursors from nerve innervation are a cellular origin of melanocytes in skin. Cell 139, 366–379.
Amoh, Y., Li, L., Katsuoka, K., Penman, S., and Hoffman, R.M. (2005). Multipotent nestin-positive, keratin-negative hair-follicle bulge stem cells can form neurons. Proc. Natl. Acad. Sci. USA 102, 5530–5534.
Arnold, K., Sarkar, A., Yram, M.A., Polo, J.M., Bronson, R., Sengupta, S., Seandel, M., Geijser, N., and Hochedlinger, K. (2011). Sox2(+) adult stem and progenitor cells are important for tissue regeneration and survival of mice. Cell Stem Cell 9, 317–329.
Biernaskie, J., Paris, M., Morozova, O., Fagan, B.M., Marra, M., Pevny, L., and Miller, F.D. (2009). SKPs derive from hair follicle precursors and exhibit properties of adult dermal stem cells. Cell Stem Cell 5, 610–623.
Brownell, I., Guevara, E., Bai, C.B., Loomis, C.A., and Joyner, A.L. (2011). Nerve-derived sonic hedgehog defines a niche for hair follicle stem cells capable of becoming epidermal stem cells. Cell Stem Cell 8, 552–565.
Danielian, P.S., Muccino, D., Rowitch, D.H., Michael, S.K., and McMahon, A.P. (1998). Modification of gene activity in mouse embryos in utero by a tamoxifen-inducible form of Cre recombinase. Curr. Biol. 8, 1323–1326.

(D–F) Sections similar to that in (C) were analyzed for the epithelial gap (D), wound width (E), and new dermal tissue (F). Student’s t test; *p < 0.05 for the comparison between Sox2fl/fl;Cre+Tam and controls (the three control groups were pooled because they were statistically similar).

(G and H) Sections similar to that in (C) were immunostained for Ki67, and the percentage of positive cells at the leading edge of the regenerating dermis (ovals in G, magnified in the right panel) was quantified (H). Arrows indicate Ki67-positive cells. One-way ANOVA; ** **p = 0.0001 relative to control groups; n = 5 C57/Bl6+Oil, 3 C57Bl6+Tam, 4 Sox2fl/fl;Cre+Oil, 7 Sox2fl/fl;Cre+Tam.

(I–K) Sections adjacent to those used for proliferation analysis were immunostained for p75NTR (I) and analyzed for the total area (J) and density (K) of p75NTR-positive cells in the wound bed. Arrows in the inset indicate p75NTR-positive cells. Student’s t test; *p < 0.05; n = 4 Sox2fl/fl;Cre+Oil and 7 Sox2fl/fl;Cre+Tam.

Scale bars, 1 mm (C), 500 μm and 125 μm (G, right and left panels, respectively), 85 μm (I), and 45 μm (inset). See also Figure S2.
Driskell, R.R., Giangreco, A., Jensen, K.B., Mulder, K.W., and Watt, F.M. (2009). Sox2-positive dermal papilla cells specify hair follicle type in mammalian epidermis. Development 136, 2815–2823.

Ellis, P., Fagan, B.M., Magness, S.T., Hutton, S., Taranova, O., Hayashi, S., McMahon, A., Rao, M., and Pevny, L. (2004). SOX2, a persistent marker for multipotential neural stem cells derived from embryonic stem cells, the embryo or the adult. Dev. Neurosci. 26, 148–165.

Jessen, K.R., and Mirsky, R. (2008). Negative regulation of myelination: relevance for development, injury, and demyelinating disease. Glia 56, 1552–1565.

Kumar, A., and Brockes, J.P. (2012). Nerve dependence in tissue, organ, and appendage regeneration. Trends Neurosci. 35, 691–699.

Le, N., Nagarajan, R., Wang, J.Y.T., Araki, T., Schmidt, R.E., and Milbrandt, J. (2005). Analysis of congenital hypomyelinating Egr2Lo/Lo nerves identifies Sox2 as an inhibitor of Schwann cell differentiation and myelination. Proc. Natl. Acad. Sci. USA 102, 2596–2601.

Madisen, L., Zwingman, T.A., Sunkin, S.M., Oh, S.W., Zariwala, H.A., Gu, H., Ng, L.L., Palmiter, R.D., Hawrylycz, M.J., Jones, A.R., et al. (2010). A robust and high-throughput Cre reporting and characterization system for the whole mouse brain. Nat. Neurosci. 13, 133–140.

Parrinello, S., Napoli, I., Ribeiro, S., Wingfield Digby, P., Fedorova, M., Parkinson, D.B., Doddrell, R.D., Nakayama, M., Adams, R.H., and Lloyd, A.C. (2010). EphB signaling directs peripheral nerve regeneration through Sox2-dependent Schwann cell sorting. Cell 143, 145–155.

Seibler, J., Zevnik, B., Küter-Luks, B., Andreas, S., Kern, H., Hennek, T., Rode, A., Heimann, C., Faust, N., Kausalmann, G., et al. (2003). Rapid generation of inducible mouse mutants. Nucleic Acids Res. 31, e12.

Sieber-Blum, M., and Hu, Y. (2008). Epidermal neural crest stem cells (EPI-NCSC) and pluripotency. Stem Cell Rev. 4, 256–260.

Srinivas, S., Watanabe, T., Lin, C.-S., William, C.M., Tanabe, Y., Jessell, T.M., and Costantini, F. (2001). Cre reporter strains produced by targeted insertion of EYFP and ECFP into the ROSA26 locus. BMC Dev. Biol. 1, 4.

Taranova, O.V., Magness, S.T., Fagan, B.M., Wu, Y., Surzenko, N., Hutton, S.R., and Pevny, L.H. (2006). SOX2 is a dose-dependent regulator of retinal neural progenitor competence. Genes Dev. 20, 1187–1202.

Van Keymeulen, A., Mascre, G., Youseff, K.K., Harel, I., Michaux, C., de Geest, N., Szpalski, C., Achouri, Y., Bloch, W., Hassan, B.A., and Blanpain, C. (2009). Epidermal progenitors give rise to Merkel cells during embryonic development and adult homeostasis. J. Cell Biol. 187, 91–100.

Yamazaki, S., Ema, H., Karlsson, G., Yamaguchi, T., Miyoshi, H., Shioda, S., Taketo, M.M., Karlsson, S., Iwama, A., and Nakachi, H. (2011). Nonmyelinating Schwann cells maintain hematopoietic stem cell hibernation in the bone marrow niche. Cell 147, 1146–1158.

Yu, K., Xu, J., Liu, Z., Sosic, D., Shao, J., Olson, E.N., Towler, D.A., and Ornitz, D.M. (2003). Conditional inactivation of FGF receptor 2 reveals an essential role for FGF signaling in the regulation of osteoblast function and bone growth. Development 130, 3063–3074.

Sox2 Regulates Skin Repair