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Review article

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Local and systemic mechanisms that control the hair follicle stem cell niche

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Supplementary Table 1 Summary of Genetic Mouse Lines for Studying the Niche–Stem Cell Crosstalk			
Genetic Mouse Lines		**Applications**	**Related Signalling Pathway Studies**
Skin stem cell-related mouse genetic tools	K15–CrePGR transgenic mouse[1]	Induces Cre-recombinase activity in hair follicle stem cells (HFSCs) upon application of the drug RU486 (also known as mifepristone).	Used to manipulate signalling pathways in HFSCs.
	K19–CreER knockin mouse[2,3]	Induces Cre-recombinase activity in HFSCs upon application of tamoxifen.	Used to study KRas signalling in Squamous cell carcinoma formation.
	Shh–CreER knockin mouse[4]	Induces Cre-recombinase activity in transit amplifying cells (TACs) upon application of tamoxifen.	Used to study Sonic hedgehog (Shh) signalling in hair regeneration.
	K14–CreER transgenetic mouse[5]	Induces Cre-recombinase activity in skin epidermis upon application of tamoxifen.	Used to manipulate signalling pathways in the epidermis.
	Inv–CreER transgenic mouse[3]	Induces Cre-recombinase activity in suprabasal cells of the interfollicular epidermis upon application of tamoxifen.	Used to study KRas signalling in squamous cell carcinoma formation.
	Tyr–CreER transgenic mouse[6,7]	Induces Cre-recombinase activity in melanocyte stem cells (McSCs) and melanocytes upon application of tamoxifen.	Used to manipulate signalling pathways in melanocyte differentiation and melanoma.
	c-Kit–CreER knockin mouse[8,9]	Induces Cre-recombinase activity in McSCs and TACs upon application of tamoxifen.	Used to manipulate signalling pathways in melanocyte differentiation and melanoma.
	Gli1–CreER knockin mouse[10]	Induces Cre-recombinase activity in upper bulge, lower bulge, hair germ and DP upon application of tamoxifen.	Used to study Shh signalling in hair regeneration.
	K5–CreER knockin mouse[11]	Tamoxifen-inducible Cre recombinase activity in K5+ epidermis.	Used to study JAK–STAT5 signalling in HFSCs.
Skin stem cell niche-related mouse genetic tools	Lef1–RFP transgenic mouse[12]	Reporter mouse expressing red fluorescent protein in dermal papilla cells.	Used to study Wnt signalling pathway in hair regeneration.
	AdipoQ–CreER transgenic mouse[13,14]	Tamoxifen-inducible Cre recombinase activity in adipocytes.	Used to study Shh and Pdgfr signalling in dermal adipocytes.

	Pdgfra–Cre transgenic mouse[13,14]	Cre recombinase activity in dermal fibroblasts	Used to study Pdgfr signalling in dermal adipocytes.
	Acan–CreER knockin mouse[15]	Tamoxifen-inducible Cre recombinase activity in dermal sheath in skin	Used to study ET-1 signalling in dermal sheath and catagen progression.
	Tbx18–Cre knockin mouse[16]	Cre recombinase activity in dermal papilla (DP) precursor cells during embryonic hair follicle morphogenesis	Used to manipulate signalling pathways in DP.
	En1–Cre knockin mouse[17]	Cre recombinase activity in En1 lineage-positive fibroblasts (EPFs)	Used to manipulate Engrailed-1 (En-1) signalling pathways in dermal fibroblast in wound healing.
	En1–CreER knockin mouse[17]	Tamoxifen-inducible Cre recombinase activity in EPFs	Used to manipulate En-1 signalling pathways in dermal fibroblast in wound healing.
	Cdh5–CreER knockin mouse[18]	Tamoxifen-inducible Cre recombinase activity in CD31+ endothelial cells	Used to study BMP4 signalling in endothelial cells in skin.
	Prox1–CreER knockin mouse[19]	Tamoxifen-inducible Cre recombinase activity in lymphatic endothelial cells	Used to manipulate signalling pathways in lymphatic vessels.
	Myh11–CreER transgenic mouse[20]	Tamoxifen-inducible Cre recombinase activity in arrector pili muscle (APM)	Used to manipulate Shh signalling pathways in APM.
	aSMA–CreER (Acta2–CreER) transgenic mouse[21]	Tamoxifen-inducible Cre recombinase activity in hair follicle dermal stem cells (hfDSCs)	Used to manipulate signalling pathways in hfDSCs.
Nerve-related mouse genetic tools	TRPV1–Cre knockin mouse[22,23]	Cre recombinase activity in specific sensory neurons that mediate heat and pain sensation	
	TRPM8–Cre knockin mouse[24]	Cre recombinase activity in specific sensory neurons that mediate cold and pain sensation	
	MrgprA3–EGFP–Cre transgenic mouse[25]	Cre recombinase activity in specific sensory neurons that mediate itch sensation	
	MrgprB4–tdTomato-2A–Cre transgenic mouse[26]	Cre recombinase activity in specific sensory neurons that mediate stroking sensation	

	MrgprD–EGFP–Cre transgenic mouse[27]	Cre recombinase activity in specific sensory neurons that mediate high threshold mechanical and pain sensation	
	Nav1.8–Cre knockin mouse[28]	Cre recombinase activity in specific sensory neurons that mediate pain sensation	
	TH–Cre transgenic mouse[29]	Cre recombinase activity in catecholaminergic sympathetic neurons	
Skin immune cell-related mouse genetic tools	Csf1r–CreER transgenic mouse[11]	Tamoxifen-inducible Cre recombinase activity in macrophages in skin	Used for manipulating OSM–JAK–STAT5 signalling between TREM2$^+$ macrophage and HFSCs.
	DEREG (Foxp3–DTR/EGFP)[11]	DT-inducible depletion of regulatory T cell	
	Foxp3–Cre knockin mouse[30]	Cre recombinase activity in regulatory T cell	Used for manipulating Jag1–Notch signalling between Treg cells and HFSCs.

1. Morris, R. J. *et al.* Capturing and profiling adult hair follicle stem cells. *Nat. Biotechnol.* **22**, 411–417 (2004).
2. Means, A. L., Xu, Y., Zhao, A., Ray, K. C. & Gu, G. A CK19CreERT Knockin Mouse Line Allows for Conditional DNA Recombination in Epithelial Cells in Multiple Endodermal Organs. *Genes. N. Y. N 2000* **46**, 318–323 (2008).
3. Lapouge, G. *et al.* Identifying the cellular origin of squamous skin tumors. *Proc. Natl. Acad. Sci.* **108**, 7431–7436 (2011).
4. Harfe, B. D. *et al.* Evidence for an Expansion-Based Temporal Shh Gradient in Specifying Vertebrate Digit Identities. *Cell* **118**, 517–528 (2004).

5. Vasioukhin, V., Degenstein, L., Wise, B. & Fuchs, E. The magical touch: Genome targeting in epidermal stem cells induced by tamoxifen application to mouse skin. *Proc. Natl. Acad. Sci.* **96**, 8551–8556 (1999).
6. Bosenberg, M. *et al.* Characterization of melanocyte-specific inducible Cre recombinase transgenic mice. *genesis* **44**, 262–267 (2006).
7. Moon, H. *et al.* Melanocyte Stem Cell Activation and Translocation Initiate Cutaneous Melanoma in Response to UV Exposure. *Cell Stem Cell* **21**, 665-678.e6 (2017).
8. Klein, S. *et al.* Interstitial cells of Cajal integrate excitatory and inhibitory neurotransmission with intestinal slow-wave activity. *Nat. Commun.* **4**, 1630 (2013).
9. Sun, Q. *et al.* A novel mouse model demonstrates that oncogenic melanocyte stem cells engender melanoma resembling human disease. *Nat. Commun.* **10**, 5023 (2019).
10. Brownell, I., Guevara, E., Bai, C. B., Loomis, C. A. & Joyner, A. L. Nerve-Derived Sonic Hedgehog Defines a Niche for Hair Follicle Stem Cells Capable of Becoming Epidermal Stem Cells. *Cell Stem Cell* **8**, 552–565 (2011).
11. Wang, E. C. E., Dai, Z., Ferrante, A. W., Drake, C. G. & Christiano, A. M. A Subset of TREM2+ Dermal Macrophages Secretes Oncostatin M to Maintain Hair Follicle Stem Cell Quiescence and Inhibit Hair Growth. *Cell Stem Cell* **24**, 654-669.e6 (2019).
12. Rompolas, P. *et al.* Live imaging of stem cell and progeny behaviour in physiological hair-follicle regeneration. *Nature* **487**, 496–499 (2012).
13. Zhang, B. *et al.* Hair follicles' transit-amplifying cells govern concurrent dermal adipocyte production through Sonic Hedgehog. *Genes Dev.* **30**, 2325–2338 (2016).

14. Rivera-Gonzalez, G. C. *et al.* Skin Adipocyte Stem Cell Self-Renewal Is Regulated by a PDGFA/AKT-Signaling Axis. *Cell Stem Cell* **19**, 738–751 (2016).
15. Heitman, N. *et al.* Dermal sheath contraction powers stem cell niche relocation during hair cycle regression. *Science* **367**, 161–166 (2020).
16. Grisanti, L. *et al.* Tbx18 targets dermal condensates for labeling, isolation and gene ablation during embryonic hair follicle formation. *J. Invest. Dermatol.* **133**, 344–353 (2013).
17. Mascharak, S. *et al.* Preventing Engrailed-1 activation in fibroblasts yields wound regeneration without scarring. *Science* **372**, eaba2374 (2021).
18. Li, K. N. *et al.* Skin vasculature and hair follicle cross-talking associated with stem cell activation and tissue homeostasis. *eLife* **8**, e45977 (2019).
19. Peña-Jimenez, D. *et al.* Lymphatic vessels interact dynamically with the hair follicle stem cell niche during skin regeneration in vivo. *EMBO J.* **38**, e101688 (2019).
20. Shwartz, Y. *et al.* Cell Types Promoting Goosebumps Form a Niche to Regulate Hair Follicle Stem Cells. *Cell* **182**, 578-593.e19 (2020).
21. Shin, W. *et al.* Dysfunction of Hair Follicle Mesenchymal Progenitors Contributes to Age-Associated Hair Loss. *Dev. Cell* **53**, 185-198.e7 (2020).
22. Cavanaugh, D. J. *et al.* Restriction of Transient Receptor Potential Vanilloid-1 to the Peptidergic Subset of Primary Afferent Neurons Follows Its Developmental Downregulation in Nonpeptidergic Neurons. *J. Neurosci.* **31**, 10119–10127 (2011).
23. Huang, S. *et al.* Lgr6 marks epidermal stem cells with a nerve-dependent role in wound re-epithelialization. *Cell Stem Cell* **28**, 1582-1596.e6 (2021).

24. Yarmolinsky, D. A. *et al.* Coding and Plasticity in the Mammalian Thermosensory System. *Neuron* **92**, 1079–1092 (2016).
25. Han, L. *et al.* A subpopulation of nociceptors specifically linked to itch. *Nat. Neurosci.* **16**, 174–182 (2013).
26. Vrontou, S., Wong, A. M., Rau, K. K., Koerber, H. R. & Anderson, D. J. Genetic identification of C-fibers that detect massage-like stroking of hairy skin in vivo. *Nature* **493**, 669–673 (2013).
27. Rau, K. K. *et al.* Mrgprd Enhances Excitability in Specific Populations of Cutaneous Murine Polymodal Nociceptors. *J. Neurosci.* **29**, 8612–8619 (2009).
28. Nassar, M. A. *et al.* Nociceptor-specific gene deletion reveals a major role for Nav1.7 (PN1) in acute and inflammatory pain. *Proc. Natl. Acad. Sci.* **101**, 12706–12711 (2004).
29. Savitt, J. M., Jang, S. S., Mu, W., Dawson, V. L. & Dawson, T. M. Bcl-x Is Required for Proper Development of the Mouse Substantia Nigra. *J. Neurosci.* **25**, 6721–6728 (2005).
30. Ali, N. *et al.* Regulatory T Cells in Skin Facilitate Epithelial Stem Cell Differentiation. *Cell* **169**, 1119-1129.e11 (2017).