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Neurobiology, Stem Cell Biology, and Immunology: An Emerging Triad for Understanding Tissue Homeostasis and Repair

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Abstract

The peripheral nervous system (PNS) endows animals with the remarkable ability to sense and respond to a dynamic world. Emerging evidence shows the PNS also participates in tissue homeostasis and repair by integrating local changes with organismal and environmental changes. Here, we provide an in-depth summary of findings delineating the diverse roles of peripheral nerves in modulating stem cell behaviors and immune responses under steady-state conditions and in response to injury and duress, with a specific focus on the skin and the hematopoietic system. These examples showcase how elucidating neuro–stem cell and neuro–immune cell interactions provides a conceptual framework that connects tissue biology and local immunity with systemic bodily changes to meet varying demands. They also demonstrate how changes in these interactions can manifest in stress, aging, cancer, and inflammation, as well as how these findings can be harnessed to guide the development of new therapeutics.

Contents

INTRODUCTION

Stem cells and immune cells are central players in tissue maintenance and repair in diverse organ systems. Stem cells self-renew and generate differentiated progeny essential for the maintenance and repair of tissues. Immune cells survey peripheral tissues, identify pathogens and damage, and mount appropriate attack or repair responses. However, tissue production and immune responses are not only localized phenomena: They often need to be coordinated with and tailored to an organism's physiological state and changing external environment.

Because the nervous system has a footprint in every organ, and because of its specialized role in sensing environmental changes, integrating diverse information across organ systems, and modulating responses systemically—all with rapid speed—it is uniquely poised to initiate and integrate local tissue changes in response to both systemic and environmental cues. Indeed, recent findings have begun to elucidate how the nervous system modulates somatic stem cell behavior or immune responses in various contexts across development, homeostasis, aging, and disease. These discoveries are fueled by technical advances in (*a*) mouse genetic tools that enable targeting of specific populations of stem cells, immune cells, or neurons (Barker et al. 2007, Beronja et al. 2010, Cavanaugh et al. 2011, Chan et al. 2017, Clausen et al. 1999, Ferron & Vacher 2005, Ito et al. 2005, Li et al. 2011, Mattiuz et al. 2018, Stirling et al. 2005); (*b*) single-cell sequencing approaches that delineate molecular changes and identify markers within heterogeneous cell populations (Baryawno et al. 2019, Chiu et al. 2014, Grover et al. 2016, Joost et al. 2020, Ma et al. 2020, Stickels et al. 2021, Tanay & Regev 2017, Tikhonova et al. 2019); and (*c*) chemogenetic and optogenetic tools that

modulate neuronal activities (Alexander et al. 2009, Armbruster et al. 2007, Boyden et al. 2005, Farrell et al. 2013, Stachniak et al. 2014). Neuro–stem cell and neuro–immune cell interactions are particularly abundant at barrier sites such as the skin and the gastrointestinal tract, as these locations are exposed to frequent insults in which rapid tissue production and immune modulation are vital (Jacobson et al. 2021, Trier et al. 2019). These interactions are also found in the bone marrow, the host site for hematopoietic stem cells (HSCs), which sit at the top of the hierarchy that produces diverse immune cell types.

Here, we discuss recent advances that showcase how the nervous system interacts with both stem and immune cells. We focus our discussions on the skin, as an example of a barrier site, and on the bone marrow, as an example of a nonbarrier site. Comparison of these two seemingly divergent systems reveals shared principles as well as interesting differences. Collectively, these advances demonstrate how the neural modulation of stem cells and immune cells is crucial for organisms to adapt to dynamic changes both locally and systemically. They also delineate experimental strategies for future investigation of these cross-system interactions and lay the foundation for the development of therapeutics that embrace a more holistic and systemic approach that treats the root cause of diseases rather than only alleviating symptoms that manifest locally.

THE ANATOMY AND FUNCTION OF THE PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system (PNS) consists of two main branches, the somatic nervous system and the autonomic nervous system. Together, they transmit peripheral signals to and from the central nervous system (CNS), which contains the brain and the spinal cord. The somatic nervous system consists of sensory neurons that enable a diverse array of sensations and motor neurons that control voluntary movement (Akinrodoye & Lui 2022). The autonomic nervous system contains three branches—the sympathetic, parasympathetic, and enteric nervous systems—that connect the CNS to all peripheral organs to regulate bodily functions and physiological responses (Karemaker 2017). For the purposes of this review, we focus on the sensory nervous system, sympathetic nervous system, and parasympathetic nervous system due to their emerging roles in regulating stem cells and immune cells.

The Sensory Nervous System

The sensory nervous system relays incredibly diverse cues from all the peripheral organs and the external environment to the CNS (**Figure 1*a***). Most sensory neuron cell bodies reside in dorsal root ganglia (DRGs) close to the spinal cord. Morphologically, most neurons have a single, long projection, called an axon, through which they deliver information to targets, and many branch-like short projections stemming from the cell body, called dendrites, through which they receive information. However, sensory neurons are uniquely pseudo-unipolar and lack dendrites. Instead, sensory axons are bifurcated—a single axon splits into two branches. One branch innervates targeted peripheral tissues to receive sensory information that is then relayed to the other branch, which delivers the information to the spinal cord. Sensory neurons are specifically attuned to detecting either innocuous or nociceptive thermal, mechanical, or chemical stimuli, with the vast majority of the DRG sensory neurons dedicated to responding to harmful stimulants (Han et al. 2013, Liu et al. 2007, Luiz et al. 2019).

Sensory neurons display a high degree of heterogeneity, and classification of both innocuous and nociceptive sensory neurons depends on cell body size, axon diameter, degree of myelination, and conduction velocity (Abraira & Ginty 2013). These neurons can be further divided into an array of subtypes based on the expression of different receptors, ion channels, signaling factors,

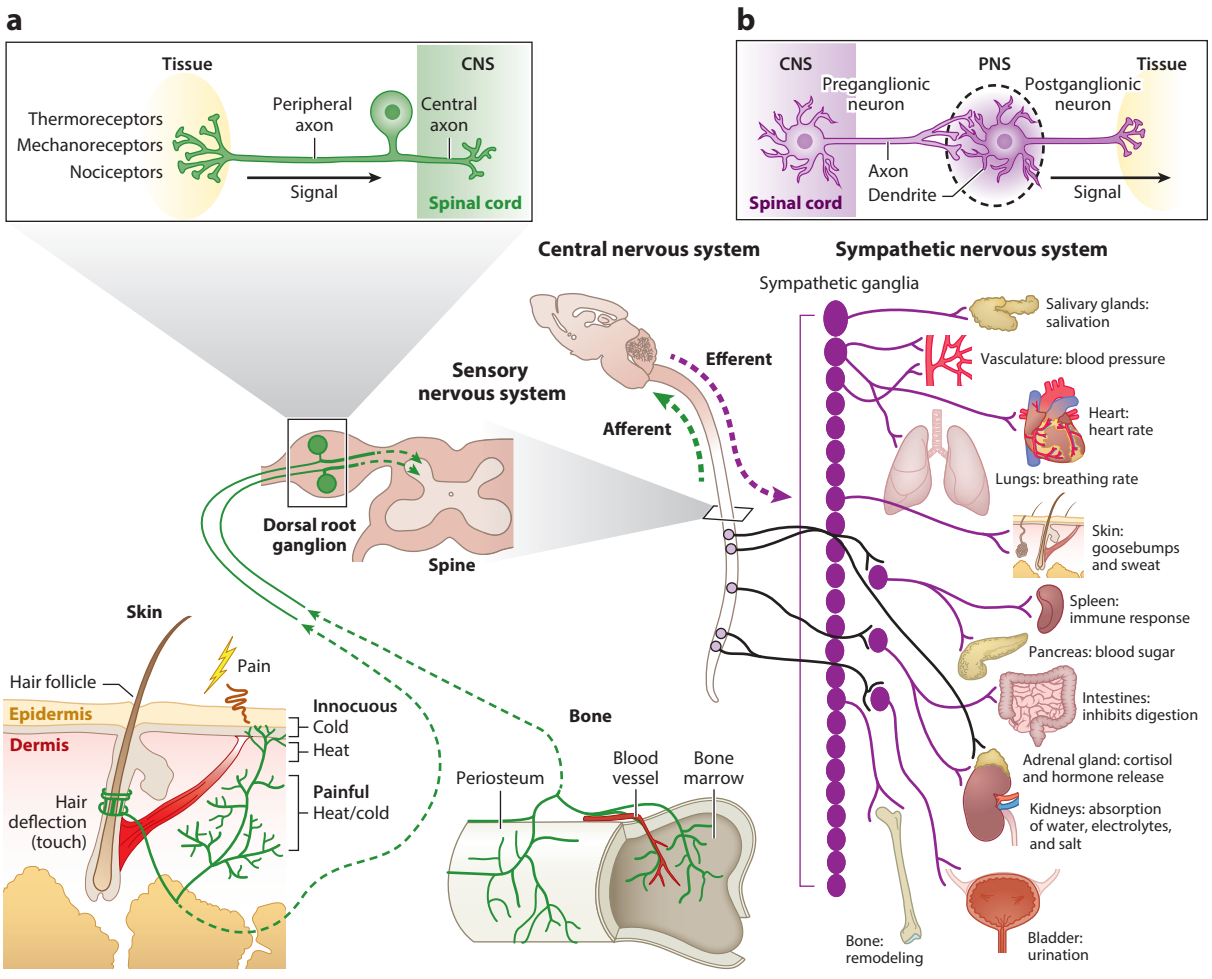


Figure 1

The peripheral nervous system (PNS). The PNS is composed of two major arms, the afferent and efferent. The afferent arm collects information from peripheral organs and relays it to the central nervous system (CNS), and then the efferent arm sends signals from the CNS back to the periphery to modulate tissue behavior and function. (*a*) Sensory neurons, located in dorsal root ganglia nestled between the spinal vertebrae, innervate diverse peripheral tissues and represent the afferent arm that brings peripheral information to the CNS. Sensory nerves display unique innervation patterns in different tissues. In the skin, sensory nerves form lanceolate endings that wrap around the hair follicle to detect touch. Dense sensory innervation of the skin with free nerve endings in the epidermis and dermis predominantly sense painful stimuli (*lightning bolt*). There are also nerves with free endings for thermal sensations, with innocuous-cold-sensing neurons located near the epidermis and heat-sensing neurons deeper in the dermis. Sensory neurons have a unique morphology with a bifurcated axon that extends one branch to peripheral tissues to detect different sensations that are then relayed to the other axonal branch that extends to the CNS. Information integrated in the CNS is relayed out through the sympathetic nervous system. (*b*) Sympathetic neurons innervate virtually every organ in the body to regulate diverse physiological processes and represent the efferent arm. The cell bodies of preganglionic sympathetic neurons are located in the spinal cord and they transmit signals from the CNS to postganglionic neurons. The cell bodies of postganglionic sympathetic neurons are located in sympathetic ganglia that form a chain near the spine. Postganglionic neurons relay the signal from presynaptic neurons to regulate innervated tissues in the periphery.

Table 1 Select examples of the functions of the peripheral nervous system in tissue regulation

	Site of action	Action	References
Sensory	Hair follicle	Gentle touch detection by hair deflection	Biemesderfer et al. 1978, Li et al. 2011, Liu et al. 2007, Vrontou et al. 2013
	Dermis and epidermis	Temperature sensing	Basbaum et al. 2009, Bautista et al. 2007, Dhaka et al. 2008, Story et al. 2003
		Injury or environmental hazards	Koizumi et al. 2004, Lumpkin & Caterin 2007
	Taste bud	Regeneration	Lu et al. 2018
	Bone marrow	Stem cell activity and differentiation	Gao et al. 2021
	Mineralized bone	Sensing tissue damage	Mach et al. 2002
Sympathetic	Secretory cells	Hormonal secretion	Karemaker 2017, Lin et al. 2021
	Smooth muscle	Control of involuntary movements	Karemaker 2017
	Hair follicle	Piloerection (goosebumps)	Furlan et al. 2016, Shwartz et al. 2020, Zhao et al. 2017
	Adipose	Thermal regulation	Sipe et al. 2017, Zeng et al. 2019
	Bone marrow	Trafficking and differentiation of hematopoietic stem cells (HSCs)	García-García et al. 2019; Maryanovich et al. 2018; Méndez-Ferrer et al. 2008, 2010
	Skin	Activation of hair follicle stem cells and depletion of melanocyte stem cells	Shwartz et al. 2020, Zhang et al. 2020
	Intestine	Promotion of tissue-protective programs in immune response	Gabanyi et al. 2016, Matheis et al. 2020
Parasympathetic	Gut	Regulation of immune cell landscape and response	de Jonge et al. 2005, Matteoli et al. 2014, Meregnani et al. 2011
	Liver	Immune response	Borovikova et al. 2000
	Bone marrow	HSC trafficking	García et al. 2013, García-García et al. 2019
	Salivary gland	Development and regeneration	Knox et al. 2010, 2013
	Prostate	Cancer formation and metastasis	Magnon et al. 2013

cytoskeletal proteins, and neuropeptides (Braz et al. 2005, Chiu et al. 2014, Dong et al. 2001, Hjerling-Leffler et al. 2007, Li et al. 2016, Usoskin et al. 2015, Zylka et al. 2005). Unique markers for sensory subtypes have enabled the generation of genetic tools to study the function of sensory populations and to visualize their complex innervation morphologies in different tissues. Sensory neurons form specific innervation patterns that are tailored to their various roles in individual tissues (**Table 1**). For example, sensory neurons in the skin form a dense network of free nerve endings within the dermis and epidermis (Vrontou et al. 2013, Wu et al. 2012, Zylka et al. 2005) (**Figure 1*a***). This weblike morphology may uniquely position them to survey environmental changes such as temperature fluctuations to regulate physiological responses. While sensory perceptions—in particular pain sensations—are important for detecting tissue damage, emerging data show that sensory neurons actively participate in tissue homeostasis and repair via modulation of stem cell behaviors and immune responses.

The Sympathetic Nervous System

Sensory neurons represent the afferent arm of the PNS—they sense stimuli in peripheral tissues and relay this information to the CNS, where the information is integrated and interpreted. A reflexive response is then delivered from the CNS back to the periphery through the sympathetic nervous system (the efferent arm) to regulate organ function. This circuit enables an immediate

response in innervated organs to adapt to internal or external changes. For example, cold detection by sensory neurons in the skin is transmitted to the hypothalamus region of the brain, which can then relay a response through cutaneous innervating sympathetic neurons to trigger goosebumps for thermal regulation (Bautista et al. 2007, Dhaka et al. 2008, Furlan et al. 2016, Shwartz et al. 2020, Story et al. 2003, Zhao et al. 2017).

The ganglia of sympathetic neurons form a bilateral chain located ventrolaterally to the spinal cord. The cell bodies of preganglionic sympathetic neurons lie in the spinal cord and extend their axons to synapse with the cell bodies of peripheral postganglionic neurons in the sympathetic ganglia (**Figure 1*b***). Postganglionic sympathetic neurons extend their axons out from the sympathetic ganglia to innervate and regulate virtually every organ in the body (**Figure 1*b***). Sympathetic neurons are constantly active under steady state to regulate physiological homeostasis—including heart rate, respiration, blood glucose levels, and digestion (Patel et al. 2015, Scott-Solomon et al. 2021, Zeng et al. 2019). The level of basal sympathetic activity also follows a circadian pattern, with different levels of basal activity associated with rest and wakefulness (Biaggioni 2008, Somers et al. 1993). Under duress, rapid elevations in sympathetic activity mobilize fight-or-flight responses—including increases in blood pressure, heart rate, and blood sugar—to enable an organism to immediately react to threats (Lin et al. 2021, Scott-Solomon et al. 2021, Sipe et al. 2017).

Being an efferent arm, postganglionic sympathetic neuronal axons innervate and transmit neuronal signals to regulate diverse target tissues in the periphery. Sympathetic axons secrete a neurotransmitter, norepinephrine, that binds to adrenergic receptors expressed by innervated tissues to regulate physiological responses (**Table 1**). Recent studies have begun to elucidate diverse roles for the sympathetic nervous system in regulating somatic stem cells and immune cells. These studies show that beyond its known roles in regulating physiology, the sympathetic nervous system also regulates tissue formation, regeneration, and repair. In fact, because sympathetic neurons are essential for modulating body physiology in response to environmental changes, they are uniquely poised to couple tissue renewal and immunity with systemic demands and changes in the external environment for optimal outcomes.

The Parasympathetic Nervous System

As a counterbalance to the sympathetic nervous system, the parasympathetic nervous system innervates many of the same targets as the sympathetic nervous system to decrease arousal after a threat has subsided and to promote rest-and-digest responses under steady state. Parasympathetic ganglia are located in close proximity to or embedded in the tissues they regulate, which they achieve through secretion of the neurotransmitter acetylcholine (Karemaker 2017). The counterbalancing nature of the sympathetic and parasympathetic nervous systems is crucial for creating an equilibrium that maintains organismal physiology. Although much remains to be learned, several interesting findings have begun to elucidate new roles of parasympathetic nerves in tissue homeostasis and cancer (**Table 1**).

NEURO–STEM CELL INTERACTIONS IN THE SKIN

The skin contains some of the most highly regenerative tissues in mammals that are maintained by distinct populations of somatic stem cells. The skin is also highly innervated with sympathetic nerves and a wide array of sensory nerves, endowing organisms with the remarkable ability to sense and respond to diverse external stimuli. Recent findings have revealed that the PNS plays a crucial role in regulating skin stem cell behaviors in tissue homeostasis and injury repair, as well as in response to stressful stimuli. Although these findings represent perhaps only the tip of the iceberg for the potentially vast complexity of nerve–stem cell interactions in the skin, they

provide a conceptual framework for understanding how neurobiology and stem cell biology can be integrated at the surface of an organism where external stimuli and insults are frequent.

Sympathetic Nerves and Hair Follicle Stem Cells: Bridging the Gap Between Stem Cells and the Environment

Tissue production and renewal are not only important for maintaining long-term organ function but are also essential for tailoring tissue growth to changing environmental demands. Interactions between sympathetic nerve endings and hair follicle stem cells (HFSCs) exemplify how the nervous system can contribute to both homeostatic maintenance and so-called on-demand growth via the direct regulation of somatic stem cells.

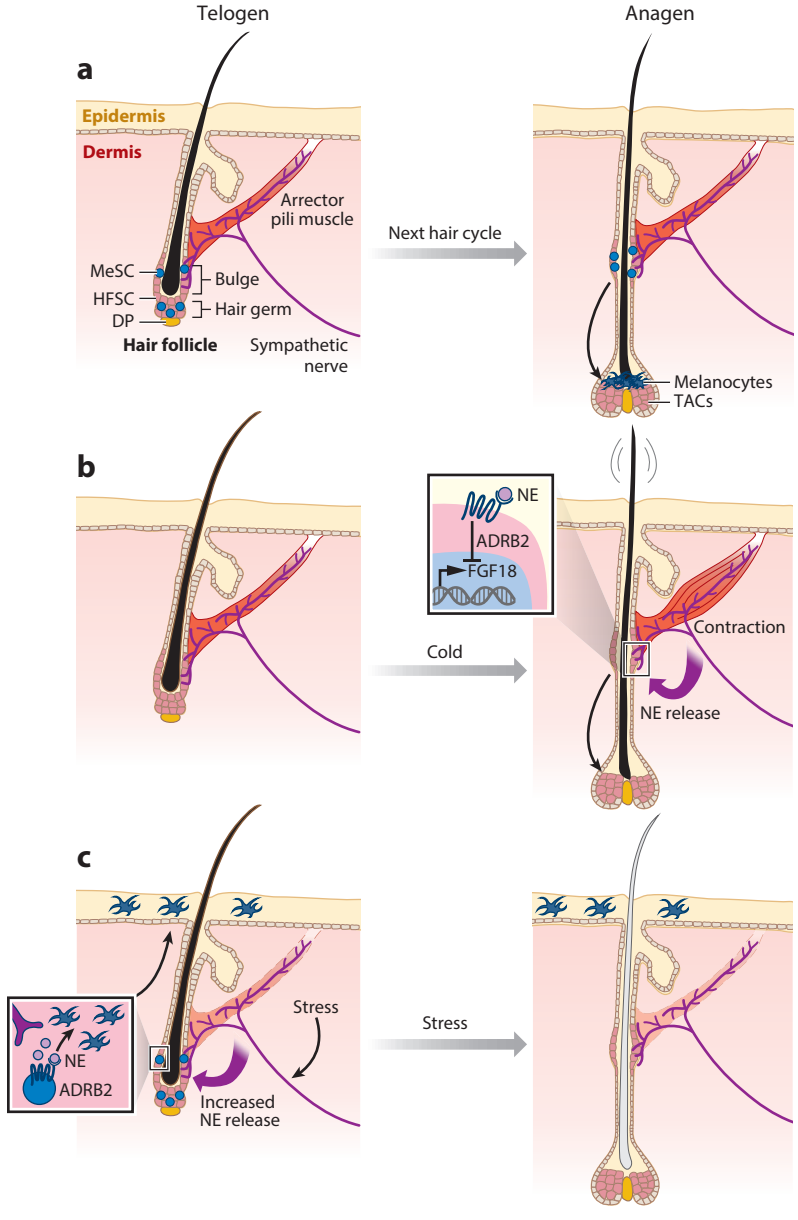
Hair is a key trait shared by all mammals. The hair follicle—the epithelial tissue hosting each hair—undergoes cycles of growth (anagen), regression (catagen), and rest (telogen). HFSCs reside in a structure called the bulge and in a small cluster below the bulge known as the hair germ. The telogen hair follicle contains only the bulge and the hair germ at the base of the hair follicle (**Figure 2*a***). Entry into anagen depends on the activation of HFSCs, which proliferate transiently to regenerate a transit-amplifying population that produces seven morphologically and molecularly distinct differentiated cell types, including the hair shaft that forms the hair (Hsu & Fuchs 2021, Zhang & Hsu 2017). The hair follicle grows deep into the dermis in anagen, while the newly formed hair grows upward and protrudes out from the skin surface (**Figure 2*a***). Anagen is the only phase in which the hair can grow longer.

Sympathetic neurons are known to innervate arrector pili muscles, a bundle of smooth muscle cells connected to HFSCs in each hair follicle (Botchkarev et al. 1999, Fujiwara et al. 2011). Cold temperature induces an elevation in the activity of the sympathetic nervous system and causes the contraction of innervated arrector pili muscles, pulling the hair to stand erect—a reaction known as piloerection, or, more familiarly, goosebumps. However, piloerection is only a rapid, first-line defense toward protection against cold. Using the arrector pili muscle as a highway, sympathetic nerves also innervate HFSCs. In mice, elevated sympathetic nerve activity in cold temperature leads to the precocious activation of HFSCs to regenerate a new hair coat (**Figure 2*b***), a mechanism that may allow animals to grow a thicker hair coat for insulation in the winter to meet seasonal demands (Shwartz et al. 2020). Besides temperature changes, activation of the sympathetic nerve activity via strong blue light stimulation also leads to hair growth, underscoring another example of how tissue production can be triggered by external environmental stimuli via the sympathetic nervous system (Fan et al. 2018).

Besides its role in stimulating HFSC activation through elevated neural activity, basal activity of the sympathetic nervous system also modulates HFSCs during normal tissue turnover. Ablation of cutaneous sympathetic nerves leads to a substantial delay in anagen entry, suggesting that low levels of sympathetic nerve activity under steady-state conditions prime HFSCs for activation. In fact, sympathetic neurons form synapse-like connections with HFSCs and modulate HFSCs directly via norepinephrine, similar to how sympathetic neurons regulate their conventional targets such as smooth muscles or glands. Norepinephrine binds to the β2-adrenergic receptors (ADRB2s) on HFSCs and downregulates the expression of a secreted signaling protein, FGF18, that normally enforces HFSC quiescence (Shwartz et al. 2020) (**Figure 2*b***). In this sense, a fast-acting, short-range neurotransmitter signal relays to a slow-acting, broad-range secreted protein signal to combine the best of both worlds—sympathetic neurons transmit rapid signals reflective of body physiology state or external environment changes, while FGF18 levels around HFSCs can further fine-tune HFSC activity for a much longer duration than does the initial neuronal impulse.

Sympathetic Nerves and Melanocyte Stem Cells: A Stressful Connection

The hair follicle also hosts another stem cell population—melanocyte stem cells (MeSCs), which are crucial for making pigments. MeSCs are derived from the neural crest and are intertwined with HFSCs in the bulge and hair germ. Like HFSCs, MeSCs are quiescent throughout most of the hair cycle and only become activated transiently during early anagen (Chang et al. 2013). Concurrent activation of HFSCs and MeSCs ensures the regeneration of a pigmented hair in anagen—HFSCs



(*Caption appears on following page*)

Figure 2 (*Figure appears on preceding page*)

Sympathetic neurons regulate two distinct populations of stem cells residing in the hair follicle under steady state, cold, and stress. (*a*) The hair follicle contains two stem cell populations of distinct origin and function. Hair follicle stem cells (HFSCs) are of epithelial origin and are located in the bulge and hair germ, abutted to the dermal papilla (DP). Melanocyte stem cells (MeSCs) arise from the neural crest and are intermingled with HFSCs in the bulge and hair germ. HFSCs and MeSCs are both quiescent during the telogen (resting) phase of the hair cycle. At the onset of the anagen (growing) phase, both stem cell populations become activated to proliferate—HFSCs produce transit-amplifying cells (TACs; also known as matrix) that regenerate a new hair and all other differentiated cells of the hair follicle. MeSCs make differentiated melanocytes that produce pigments that color the hair. (*b*) Basal sympathetic nerve activity primes HFSCs for activation via the neurotransmitter norepinephrine (NE). NE binds to β2-adrenergic receptors (ADRB2s) on the surface of HFSCs to downregulate expression of a quiescence-promoting secreted protein, FGF18. Following cold exposure, elevated sympathetic nerve activity not only induces goosebumps (piloerection) but also accelerates HFSC activation and promotes new hair growth. (*c*) Following strong acute stress, hyperactivated sympathetic nerves secrete an excess of NE around the bulge, which binds to ADRB2s on MeSCs. Activated ADRB2 signaling in MeSCs causes them to hyperproliferate, differentiate, and be permanently depleted from the bulge. Loss of MeSCs leads to the production of an unpigmented hair in the next hair cycle.

produce the hair follicle and the hair, while MeSCs produce differentiated melanocytes that color the hair (Lu et al. 2020, Rabbani et al. 2011) (**Figure 2*a***). In the absence of MeSCs, the hair newly formed in anagen becomes unpigmented, a process commonly referred to as hair graying.

We are all familiar with the maxim that stress turns hair gray or have heard anecdotes of someone's hair turning gray following a highly stressful event. Recently, sympathetic neurons have been shown to drive stress-induced hair graying. Under strong acute stress in mice, the sympathetic nervous system becomes highly activated to trigger the fight-or-flight response. Excess norepinephrine secreted from the sympathetic axon terminals near the hair follicle binds to the ADRB2 receptors on MeSCs and triggers the cells' permanent depletion from the hair follicle within days (Zhang et al. 2020) (**Figure 2*c***). Norepinephrine triggers a similar response in human MeSCs in cultured hair follicle explants (Rachmin et al. 2021). This rapid depletion of MeSCs demonstrates how an acutely stressful event can have detrimental and irreversible consequences on tissue regeneration by causing the rapid loss of a somatic stem cell population through overactivation of the sympathetic nervous system. Stress is often associated with damage to multiple organ systems (Choi et al. 2021, Shukla et al. 2021, Sivamani et al. 2009, Song et al. 2018, Yirmiya et al. 2006), but how a psychological state influences tissue changes at the cellular and molecular levels remains unclear. It will be interesting to investigate if other stress-related tissue changes also involve changes in stem cell populations linked to the PNS.

In addition to being associated with stress, hair graying also occurs with aging. Natural aging is marked by a decline in tissue homeostasis and regeneration, which in part is attributed to changes in somatic stem cells. Interestingly, patients who underwent partial sympathectomy (removal of sympathetic innervation) developed fewer unpigmented hairs on the side that no longer had sympathetic innervation with age (Lerner 1966, Ortonne et al. 1982). Therefore, the sympathetic nervous system could contribute to the age-related gradual loss of MeSCs, and hyperactivation of the sympathetic nervous system under acute stress may accelerate this process. Aged skin also shows many deficits in regeneration, including a decline in hair follicle regeneration and a delay in wound healing, with some of these defects also seen under stress (Choi et al. 2021; Ge et al. 2020; Keyes et al. 2013, 2016). Further work investigating the similarities and differences between the stress response and the aging process will provide new insights into how the PNS contributes to the tissue decline seen with both processes and identify potential ways to halt or reverse these changes.

The Role of Sensory Neurons During Wound Repair

Normal tissue turnover utilizes discrete stem cell populations for compartment-specific regeneration. Following injury, individual stem cell populations often lose their regionally restricted behavior and exhibit a high degree of plasticity for tissue repair. This plasticity is seen in the skin epithelium, which contains the stratified epidermis, the hair follicle, and the isthmus region connecting the hair follicle with the epidermis. Under steady state, the epidermis is maintained by epidermal stem cells (EpSCs) located at the basal layer of the epidermis. Upon injury, in addition to EpSCs, cells from the hair follicle and the isthmus region become activated and migrate to the epidermis to participate in the repair process (Brownell et al. 2011, Huang et al. 2021a, Ito et al. 2005) (**Figure 3*a***). Interestingly, when sensory nerves are ablated, the contribution of hair follicle cells to the recovered epidermis after wounding is reduced (Brownell et al. 2011), suggesting a role for sensory nerves in mobilizing hair follicle cells for wound repair.

Sensory nerves also innervate a subset of EpSCs marked by LGR6 (leucine-rich repeat–containing G protein–coupled receptor 6). LGR6$^{(+)}$ and LGR6$^{(-)}$ EpSCs behave similarly during normal epidermal turnover. However, upon wounding, LGR6$^{(+)}$ EpSCs proliferate faster than the LGR6$^{(-)}$ EpSCs and are the early responders for reepithelialization (**Figure 3*b***). Surgical ablation of sensory innervation delays wound closure at the early phase due to a decrease in LGR6$^{(+)}$ EpSC proliferation, underscoring the importance of sensory innervation in mobilizing EpSCs in the early stage of wound repair.

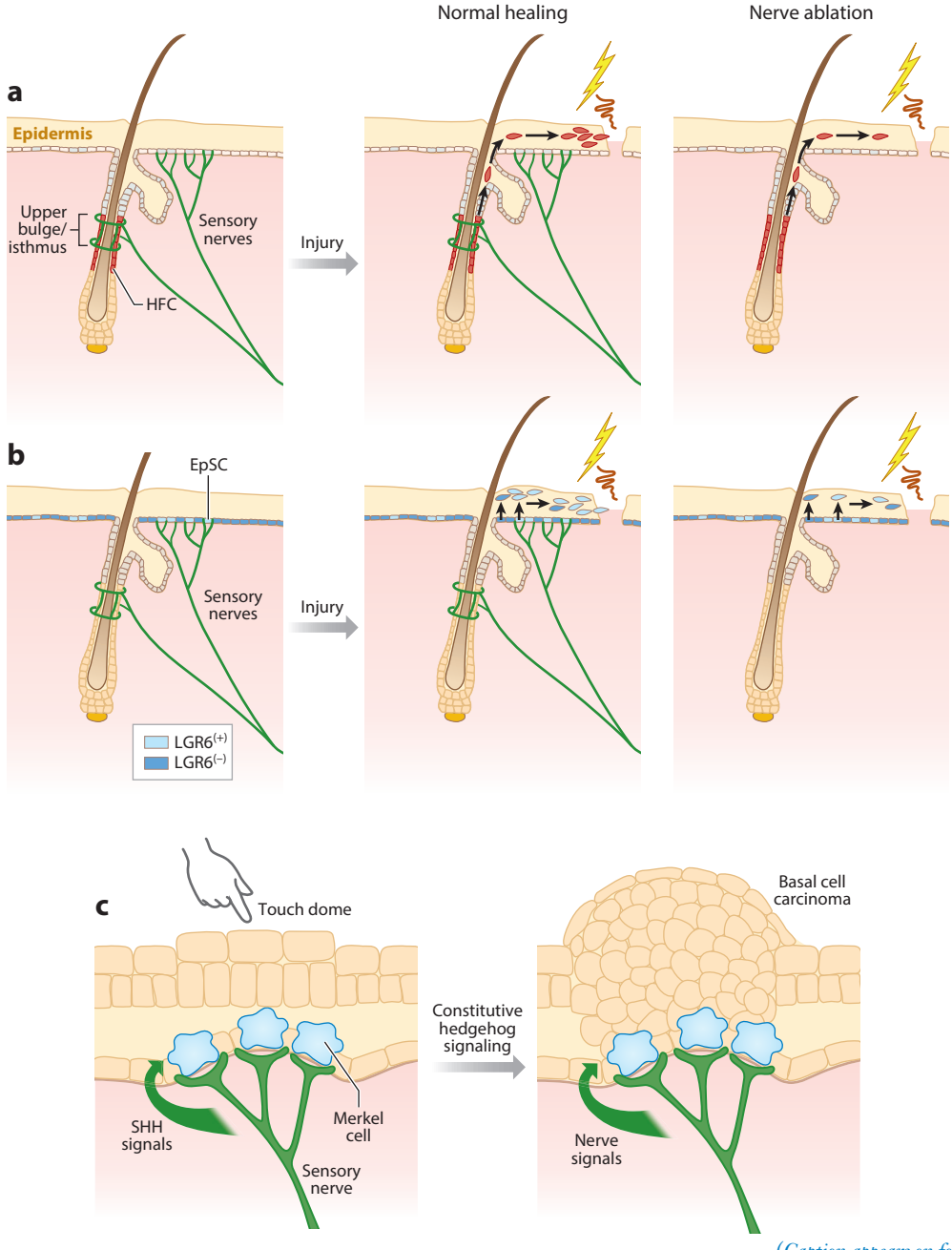
Peripheral neuropathy (loss of peripheral nerves) and chronic wounds are two common morbidities experienced by diabetic patients and cancer patients undergoing chemotherapy (Kanat et al. 2017, McNees & Meneses 2007, Volmer-Thole & Lobmann 2016). The discovery that peripheral nerves may play a role in wound healing suggests that these two morbidities may be more related than previously anticipated. Delineating the specific types of peripheral neurons and the signals they send to modulate the healing process may inform the development of new treatments for chronic wounds.

Sensory Nerves Modulate Cancer Development and Progression: The Touch Dome as a Cancer Hot Spot

The touch dome is a tiny, self-contained epidermal compartment critical for perceiving gentle touch. A touch dome is composed of basal epidermal cells, Merkel cells (specialized mechanoreceptors derived from touch dome epidermal cells), and innervation from Aβ sensory neurons [a type of low-threshold mechanoreceptor (LTMR)] (Iggo & Muir 1969, Jenkins et al. 2019, Li et al. 2011, Morrison et al. 2009, Nguyen et al. 2018, Van Keymeulen et al. 2009) (**Figure 3*c***). Denervation leads to changes in touch dome morphology and the loss of Merkel cells over time, suggesting that neuronal signals are important for Merkel cell maintenance (English et al. 1983, Xiao et al. 2015). Sonic hedgehog (SHH) was identified as a sensory nerve–derived signal that partially contributes to touch dome homeostasis and Merkel cell formation (Perdigoto et al. 2016; Xiao et al. 2015, 2016). Interestingly, regions of the epidermis containing touch domes are often hot spots for basal cell carcinoma (BCC) compared to the rest of the epidermis. BCC is the most prevalent cancer in the world and is caused by mutations that lead to a constitutive activation of the hedgehog pathway (**Figure 3*c***). Loss of sensory nerves attenuates touch dome–derived BCCs, suggesting a role for sensory nerves, and potentially nerve-derived SHH, in modulating BCC formation (Peterson et al. 2015).

Many solid tumors are highly innervated (Magnon et al. 2013, Rabben et al. 2016, Seifert & Spitznas 2002). Interestingly, solid tumors with denser peripheral innervation are often associated with poorer prognoses (Hayakawa et al. 2017, Kamiya et al. 2019, Madeo et al. 2018, Pan et al.

2021, Venkatesh et al. 2017). Although much remains to be learned about the role of peripheral nerves in cancer, several studies have shown improved prognosis in breast cancer mouse models and human melanoma patients following treatment with β-blockers (drugs that dampen sympathetic neuron signaling) (De Giorgi et al. 2018, Glasner et al. 2010). Future studies exploring the dependence of tumor formation and progression on peripheral nerves could uncover how neuromodulation influences cancer and identify potential new therapies.



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

Sensory neurons mobilize stem cells in the hair follicle and epidermis for wound repair. (*a*) Sensory neurons wrap around hair follicles to regulate the migration of hair follicle cells (HFCs) from the upper bulge/isthmus toward the epidermis upon injury (*lightning bolt*). The absence of sensory nerves reduces the contribution of HFCs to epidermal repair. (*b*) Sensory neurons innervate the epidermis in regions containing leucine-rich repeat–containing G protein–coupled receptor 6 [LGR6$^{(+)}$] epidermal stem cells (EpSCs). Following injury, sensory innervation drives the rapid mobilization of LGR6$^{(+)}$ EpSCs to begin reepithelialization. Upon denervation, LGR6$^{(+)}$ EpSCs lose their rapid activation status and contribute equally with LGR6$^{(-)}$ EpSCs to wound repair. (*c*) The touch dome is a tiny structure composed of basal epidermal cells and specialized mechanosensing Merkel cells. Merkel cells depend on sensory nerve–derived Sonic hedgehog (SHH) for maintenance. Constitutive SHH signaling induces basal cell carcinoma formation that is dependent on signals from sensory nerves for development.

PERIPHERAL NERVE REGULATION OF HEMATOPOIETIC STEM CELLS AND THE BONE MARROW

HSCs produce and maintain all blood cell types (Haas et al. 2018, Olson et al. 2020, Wang & Wagers 2011) (**Figure 4**). HSCs reside primarily in the bone marrow, but they also rhythmically

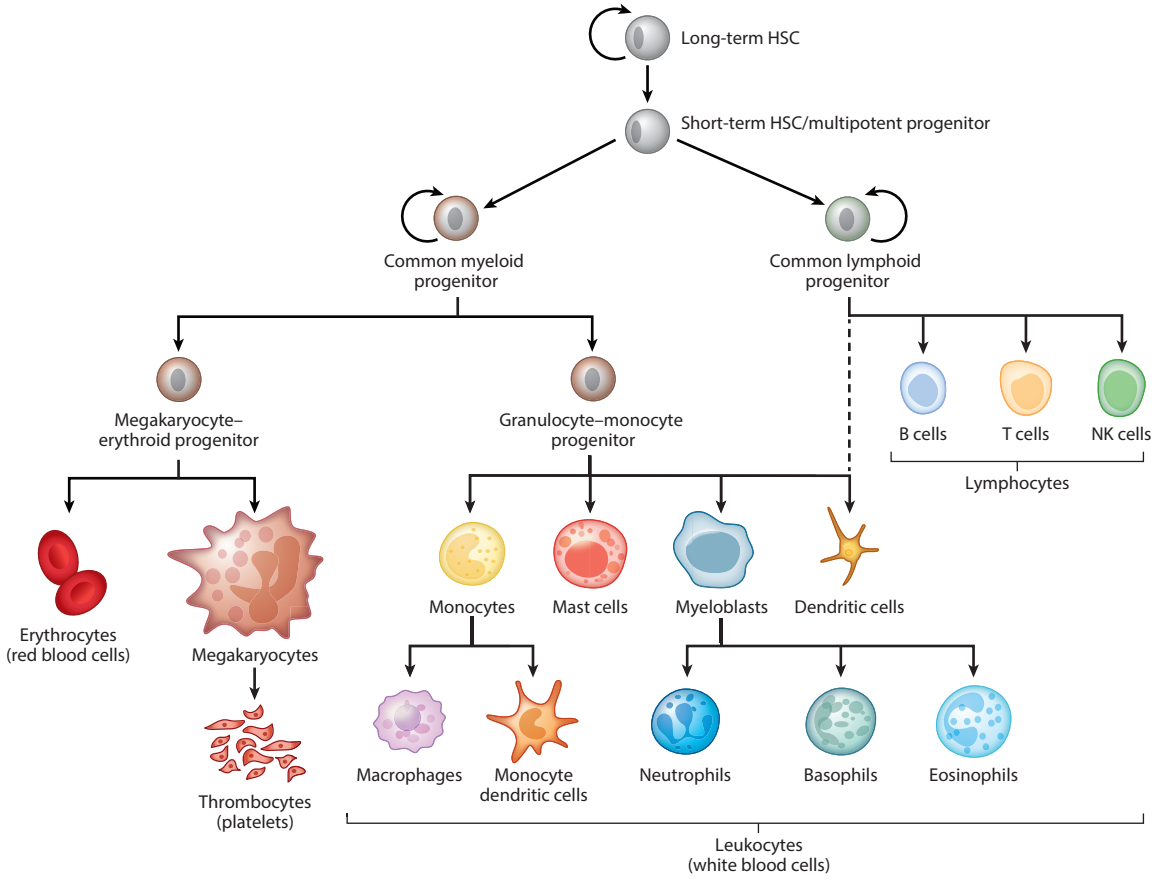


Figure 4

The hematopoietic stem cell (HSC) lineage. HSCs give rise to multipotent progenitors that then produce myeloid or lymphoid progeny downstream. The myeloid progenitor gives rise to all monocytes and granulocytes as well as to erythrocytes and megakaryocytes that produce platelets. Macrophages are monocytes that have migrated from the bloodstream into tissues. The lymphoid progenitor produces T cells, B cells, and natural killer (NK) cells.

egress from the bone marrow and circulate in the bloodstream under steady state. Bone marrow is a highly vascularized tissue filled with diverse mesenchymal cells that regulate HSC self-renewal and egress. It is also densely innervated by peripheral autonomic and sensory neurons. Studies have revealed a significant contribution of this dense innervation network to the regulation of HSCs and their progeny.

Sympathetic Neurons and Hematopoietic Stem Cells: A Daily Rhythm

Many stem cells display rhythmic behaviors that may contribute to their maintenance and functionality in tissue renewal. One of the most well-described oscillatory behaviors is the daily egress of HSCs from the bone marrow. The sympathetic nervous system regulates the proliferation and differentiation of HSCs as well as the migration of HSCs and their progeny in and out of the bone marrow (Katayama et al. 2006, Lucas et al. 2008, Méndez-Ferrer et al. 2008, Scheiermann et al. 2012). Sympathetic neurons were first shown to be required for HSC egress from the bone marrow under the stimulation of G-CSF (granulocyte colony-stimulating factor), a cytokine used to mobilize the release of HSCs from the bone marrow for transplantation purposes (Katayama et al. 2006). Emerging evidence now suggests basal autonomic activity is an essential regulator of the circadian release of HSCs into the bloodstream. The number of circulating HSCs and progenitors oscillates throughout the day, peaking during the early resting phase and reaching a low during active wakefulness (Lucas et al. 2008). Cyclic egress of HSCs from the bone marrow is mediated by the rhythmic release of norepinephrine from the sympathetic nerve terminals innervating the bone marrow (**Figure 5**). This rhythmic pattern is abolished in chemically sympathectomized mice or mice lacking the β3-adrenergic receptor (ADRB3) (Méndez-Ferrer et al. 2008), suggesting a key role for sympathetic nerves in orchestrating rhythmic stem cell behavior according to the circadian clock. Instead of regulating HSCs directly, sympathetic nerves suppress the expression of chemokine (C-X-C motif) ligand 12 (CXCL12) by the mesenchymal stromal cells in the niche, which promotes HSC egress from the bone marrow (Méndez-Ferrer et al. 2008, 2010). A recent study further suggests the parasympathetic nervous system modulates the activity of the sympathetic nervous system to reduce the egress of HSCs and leukocytes from the bone marrow during wakefulness (García-García et al. 2019) (**Figure 5**), which exemplifies the counterbalancing nature of the two branches of the autonomic nervous system in regulating stem cell behaviors. Harnessing this rhythmic nature may lead to significantly higher yields of HSCs clinically if the blood is harvested during the peak of HSC release. It may also inform optimal treatment regimens for leukemia or inflammatory diseases.

Sympathetic Neurons in Stress, Chemotherapy, and Aging

Interestingly, the same sympathetic nerve–stromal axis that regulates the rhythmic HSC behavior is further activated under stress. When mice are subjected to chronic stress, elevated sympathetic nerve activity causes enhanced norepinephrine release, which in turn reduces CXCL12 levels in the stroma. These changes lead to the activation of the most quiescent HSC populations and the release of both HSCs and leukocytes (in particular neutrophils and inflammatory monocytes) into the bloodstream (Heidt et al. 2014) (**Figure 6*a***). In fact, the same responses were detected in medical residents during their stressful shift hours at a hospital intensive care unit (Heidt et al. 2014). Increased leukocytes in the bloodstream can be advantageous for fighting infections. However, the increased output of neutrophils and inflammatory monocytes also promotes plaque formation that can cause atherosclerosis, myocardial infarction, and stroke (Heidt et al. 2014). Additionally, increased monocyte production and release in response to chronic stress is associated with prolonged exacerbations in neuropsychiatric disorders, including anxiety (McKim et al. 2016, Powell et al. 2013). Going forward, it will be important to investigate how long-term

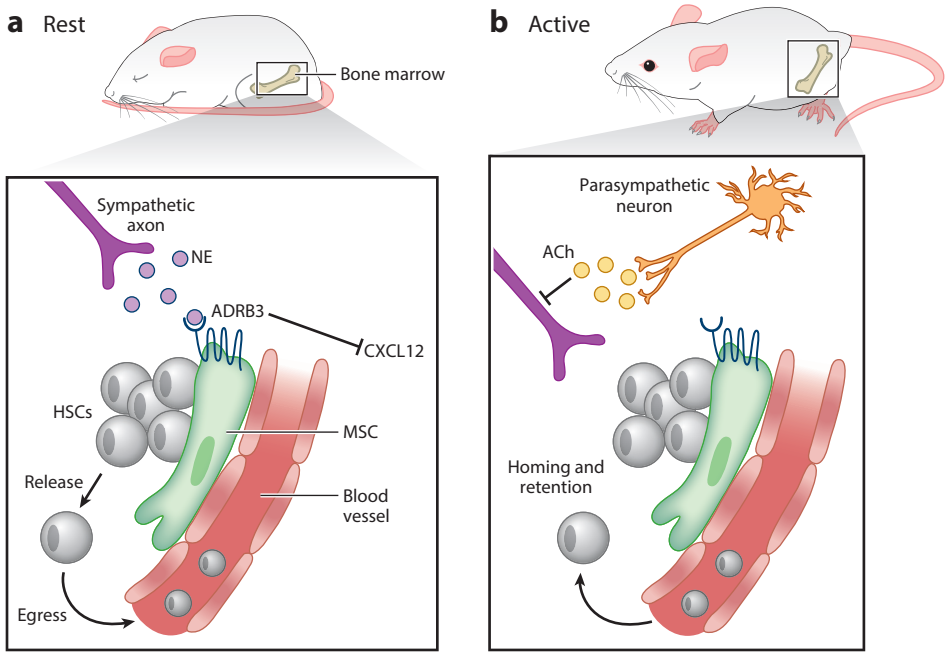


Figure 5

Autonomic nerves regulate hematopoietic stem cell (HSC) trafficking in the bone marrow. (*a*) Sympathetic activity regulates the circadian egress of HSCs and progenitors. Norepinephrine (NE) released from sympathetic terminals binds to the β3-adrenergic receptors (ADRB3s) on mesenchymal stromal cells (MSCs) to downregulate the expression of chemokine (C-X-C motif) ligand 12 (CXCL12) and permit HSC release into circulation during rest. (*b*) Parasympathetic signaling from the central nervous system regulates the circadian retention of HSCs and progenitors in the bone marrow. Acetylcholine (ACh) signals released from central parasympathetic neurons repress sympathetic activity to promote homing and retention of HSCs during wakefulness.

elevations in autonomic activity affect HSC populations and progeny and the downstream implications of these effects on disease development and progression.

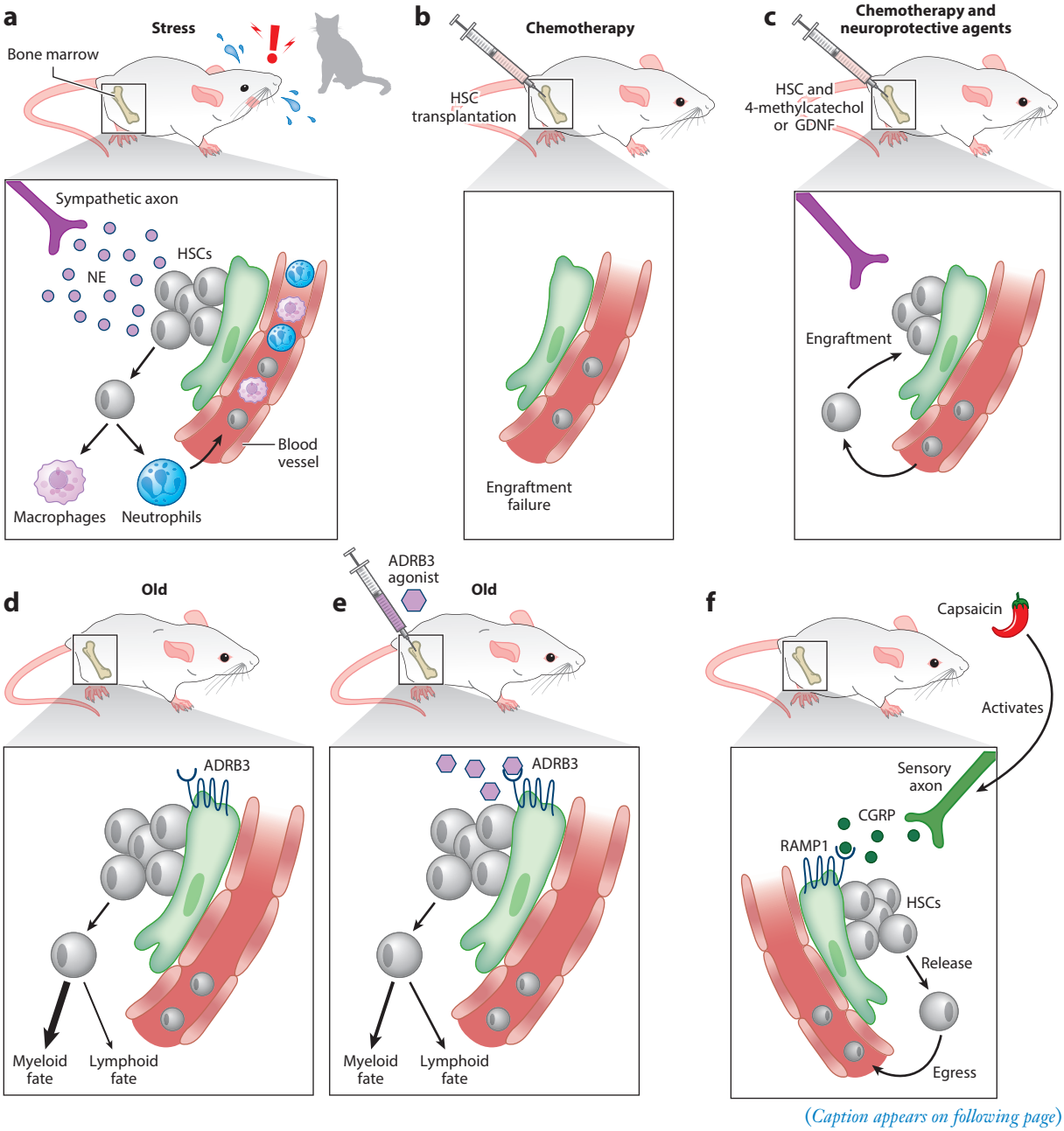
Sympathetic neuropathy following therapeutic drug treatments can also have pathological consequences. For example, many chemotherapeutic agents such as cisplatin damage sympathetic innervation (Adams et al. 2015, Lucas et al. 2013). Loss of sympathetic innervation causes significant alterations to the bone marrow microenvironment that can impair HSC engraftment following transplantation (**Figure 6*b***). Prevention of sympathetic nerve damage following cisplatin treatment improves HSC recovery (Lucas et al. 2013). Cisplatin and other platinum-based chemotherapeutic compounds are known neurotoxins that can lead to severe peripheral neuropathy beyond their impact on sympathetic neurons (Argyriou et al. 2012). Future studies could explore how loss of peripheral innervation may contribute to other long-term side effects seen with chemotherapy and if preventing neuronal death mitigates them.

With age, HSCs display a decline in regeneration potential and a shift to a myeloid-biased fate. Coinciding with these HSC changes, the bone marrow also displays a significant loss in sympathetic innervation. This age-related HSC dysfunction can be partially rescued with an ADRB3 agonist, suggesting that decreases in norepinephrine signaling through loss of sympathetic innervation in the bone marrow influence the aging process of HSCs (Maryanovich et al. 2018) (**Figure 6*c***). Collectively, these findings suggest that sympathetic nerve degeneration contributes

to several HSC pathologies. It will be interesting to explore if changes in peripheral nerve innervation is a common theme among different organ systems during aging, and if these nerve alterations contribute to age-related stem cell declines.

Sensory Nerves and Hematopoietic Stem Cells: Spicing Things Up

The bone marrow is also innervated with sensory nerves, in particular nociceptive neurons. Sensory nerves innervating the bone marrow work in concert with sympathetic nerves to regulate



(Caption appears on following page)

Figure 6 (*Figure appears on preceding page*)

Alterations in peripheral nerve activity can dysregulate hematopoietic stem cells (HSCs) to contribute to disease, but they may also have the potential to be harnessed for therapies. (*a*) Chronic stress elevates sympathetic activity, causing aberrant mobilization of HSCs. Excessive norepinephrine (NE) increases the release of HSCs and leukocytes from the bone marrow, leading to higher circulating levels of these cells in the blood. (*b*) Sympathectomy by chemotherapeutic agents such as cisplatin impairs HSC engraftment following transplantation. (*c*) Pretreatment with the neuroprotective agents 4-methylcatechol or glia-derived neurotrophic factor (GDNF) prevents cisplatin-induced loss and improves HSC engraftment. (*d*) Reduction or loss of sympathetic innervation in the bone marrow during aging alters HSCs toward a myeloid-biased fate. (*e*) Activation of the β3-adrenergic receptor (ADRB3) in the niche with an agonist partially rescues the age-related HSC phenotype. (*f*) Nociceptive sensory neurons directly regulate HSCs to promote their egress. Capsaicin can activate nociceptive neurons to increase release of the neuropeptide calcitonin gene–related peptide (CGRP). CGRP binds to receptor activity–modifying protein 1 (RAMP1) expressed by HSCs to promote their release from the bone marrow.

HSCs. Dual ablation of sympathetic neurons and nociceptive neurons leads to a significant HSC expansion in the bone marrow and biases hematopoiesis toward a myeloid fate, a phenotype not seen with the ablation of sympathetic neurons or nociceptive neurons alone. By contrast, chemical sympathectomy alone specifically leads to lower lymphopoiesis without affecting myeloid lineages (Gao et al. 2021). These results suggest that different peripheral neurons may preferentially regulate different subsets of HSC populations.

Additionally, similar to sympathetic neurons, nociceptive neurons also regulate G-CSF-induced HSC egress from the bone marrow. However, in contrast to the sympathetic nerves, which regulate the egress process indirectly via their influence on the stroma, sensory neurons directly regulate HSCs via secretion of the neuropeptide calcitonin gene-related peptide (CGRP) (**Figure 6*d***). Interestingly, feeding mice with food containing capsaicin (an active component of chili peppers), which activates nociceptive neurons via binding to receptor activity–modifying protein 1 (RAMP1), can enhance G-CSF-induced HSC mobilization (Gao et al. 2021). Together, these findings suggest multiple nerve-based strategies that could be exploited to promote HSC egress for clinical uses.

Autonomic Imbalance: How Stress Hurts the Bones

Besides regulating HSCs residing in the bone marrow, the nervous system also has an interesting role in regulating the bone tissue itself. Sympathetic activity supports bone resorption by promoting the differentiation of progenitors to osteoclasts, while parasympathetic activity promotes bone accrual by inhibiting osteoclasts through activation of apoptotic pathways for bone accrual (Bajayo et al. 2012, Elefteriou et al. 2005). Patients with neuropsychiatric disorders, neurodegenerative diseases, and epilepsy, all of which dysregulate autonomic activity, commonly have low bone mass and osteoporosis (Brady et al. 2019; Melton et al. 1994; Moen et al. 2011; Yirmiya et al. 2006; Zhou et al. 2011, 2014). Chronic depression is also associated with a decrease in bone mass that may be caused by stress-induced elevation in sympathetic activity (Yirmiya et al. 2006). By contrast, traumatic brain injury that decreases sympathetic activity is associated with an increase in bone formation (Tam et al. 2008). Future work to uncover the mechanisms by which sympathetic neurons regulate these different changes in the bone will clarify how stress impacts bones.

NEUROIMMUNE INTERACTIONS

Similar to the nervous system, the immune system is highly specialized for sensing and responding to the environment. HSCs sit at the top of the hierarchy to produce and maintain an array of cell types that constitute the immune system (**Figure 4**). Emerging evidence has revealed various interactions between the immune system and the nervous system during development, upon injury, and in disease (Chen et al. 2021, Chu et al. 2020, Godinho-Silva et al. 2019, Ordovas-Montanes

et al. 2015, Udit et al. 2022, Veiga-Fernandes & Mucida 2016). Here, we focus on how the PNS regulates immune cell trafficking from the bone marrow and the lymph nodes to peripheral tissues and how these neuroimmune interactions impact skin immunity.

Neural Regulation of Immune Cell Trafficking

Under steady state, low levels of leukocytes (white blood cells)—including granulocytes (neutrophils, eosinophils, and basophils), monocytes, and lymphocytes (T and B cells)—constantly circulate between the bone marrow, lymph nodes, and peripheral organs. This circulation is part of the immunosurveillance that maximizes encounters between pathogens and immune cells (Massberg et al. 2007). The number of leukocytes in peripheral tissues varies throughout the day, coinciding with rhythmic oscillations in sympathetic nerve activity (Brown & Dougherty 1956, Halberg et al. 1953, Scheiermann et al. 2012). Inflammation—the body's response to infection or injury—often involves substantial leukocyte infiltration to the affected sites. Leukocyte recruitment still exhibits strong oscillations even under inflammation, and different numbers of leukocytes can directly impact the outcome of inflammatory diseases (Scheiermann et al. 2012). Ablation of sympathetic innervation in peripheral tissues abolishes the circadian fluctuation of immune cells in the periphery, in particular macrophages and neutrophils, suggesting that sympathetic activity regulates leukocyte retention (Scheiermann et al. 2012) (**Figure 7*a***). ADRB2 signaling is also important for regulating lymphocyte egress from lymph nodes to peripheral tissues (Nakai et al. 2014) (**Figure 7*b***). The rhythmic pattern of leukocyte recruitment allows more leukocytes to be available at peripheral tissues during daily active periods, when injuries and infections are more likely to occur.

Interestingly, the neuroanatomy of acupuncture—an ancient practice involving stimulating specific regions of somatic tissues to modulate distant organs or whole-body physiology—has gradually begun to reveal the significance of the neuroimmune axis in tissue repair (Ma 2020). Although many open questions remain about the mechanisms of acupuncture, it has been shown to modulate inflammatory responses in part via the sympathetic nervous system and parasympathetic nervous system (Liu et al. 2020, 2021). The neuroanatomical basis for acupuncture provides a compelling demonstration of how the interconnectivity of neurocircuitry can be leveraged to achieve desired modulations at a systemic level or at a distal organ far from the stimulation site.

Besides the autonomic nervous system, nociceptive sensory neurons also innervate the lymph node and may modulate the trafficking of leukocytes both directly and indirectly via endothelial cells or stroma in the lymph node (Huang et al. 2021b). These findings suggest potentially diverse roles for peripheral nerves in regulating the migratory behavior of immune cells and their retention in different tissues.

Neuroimmune Interactions in the Skin

As the first line of defense against environmental insults and hazards, the skin functions as a crucial barrier against infection. Immune cells in the skin must remain vigilant, and they are poised to sense and respond to intruding pathogens, including bacteria, fungi, viruses, and parasites. Emerging evidence has suggested that nociceptive sensory neurons both transmit painful sensations and orchestrate immune responses by directly sensing pathogens. For example, in *Candida albicans* skin infections—a type of fungal infection—fungal-derived β-glucan binds to the Dectin-1 receptor expressed by nociceptive neurons (**Figure 8*a***). The activation of nociceptive neurons leads to pain sensation and triggers the release of the neuropeptide CGRP, which through a relaying cascade via dermal dendritic cells eventually drives interleukin-17 (IL-17) production in γδ T cells (Cohen

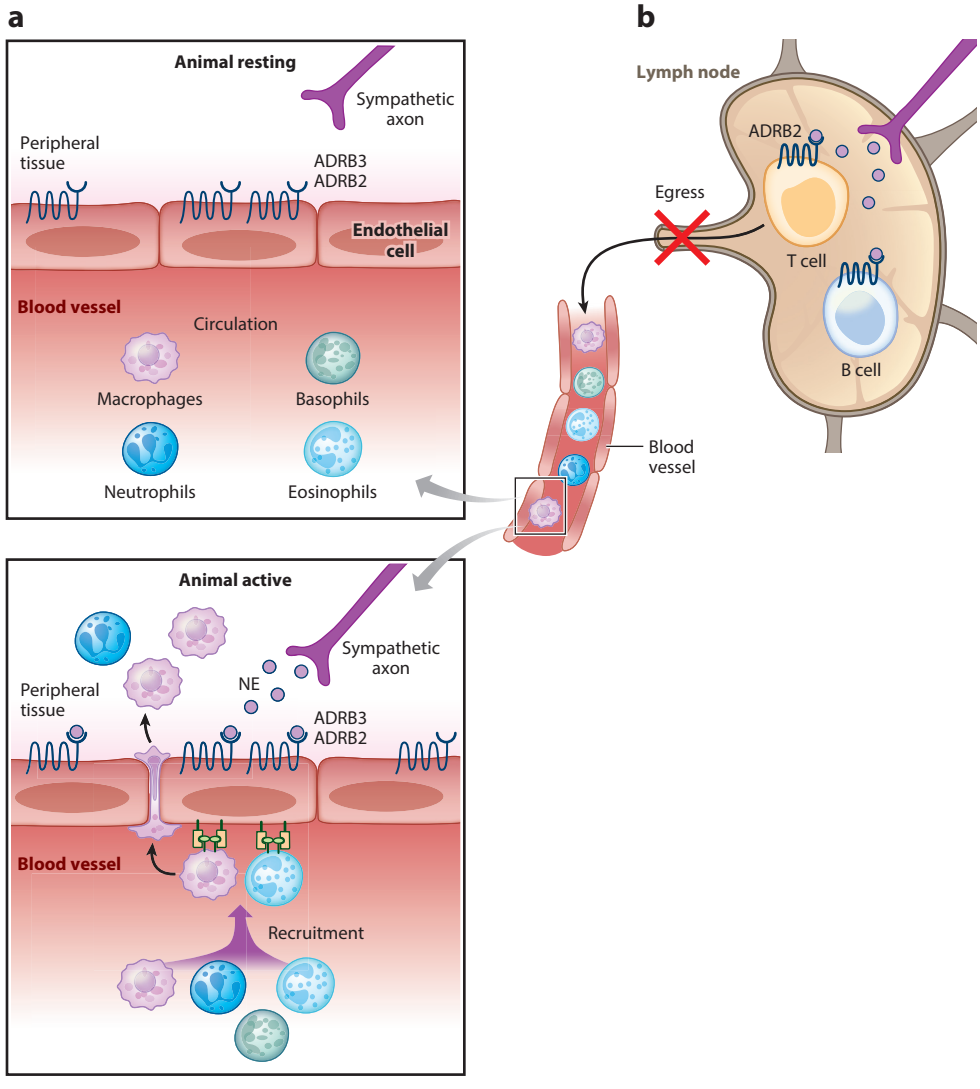


Figure 7

Sympathetic nerves regulate immune cell trafficking. (*a*) Sympathetic nerves regulate the circadian recruitment of leukocytes to peripheral tissues. (*Top*) Leukocytes circulate in the blood when sympathetic activity is low during rest. (*Bottom*) During wakefulness, sympathetic nerves release norepinephrine (NE) that binds and signals through ADRB2 and ADRB3 (β2- and β3-adrenergic receptors) in vascular endothelial cells to increase the expression of extracellular proteins that tether circulating leukocytes for retention and infiltration into peripheral tissues. (*b*) Sympathetic nerves also directly regulate the trafficking of lymphocytes. The activation of ADRB2 receptors on T cells and B cells prevents their egress from lymph nodes.

et al. 2019, Maruyama et al. 2018). IL-17 is critical for eliciting protective immunity against *C. albicans*. Therefore, patients who are defective in IL-17 responses [such as patients with AIDS (autoimmune deficiency syndrome)] are particularly susceptible to *C. albicans* infection (Kashem et al. 2015). Optogenetic activation of cutaneous nociceptive sensory neurons in the absence of tissue

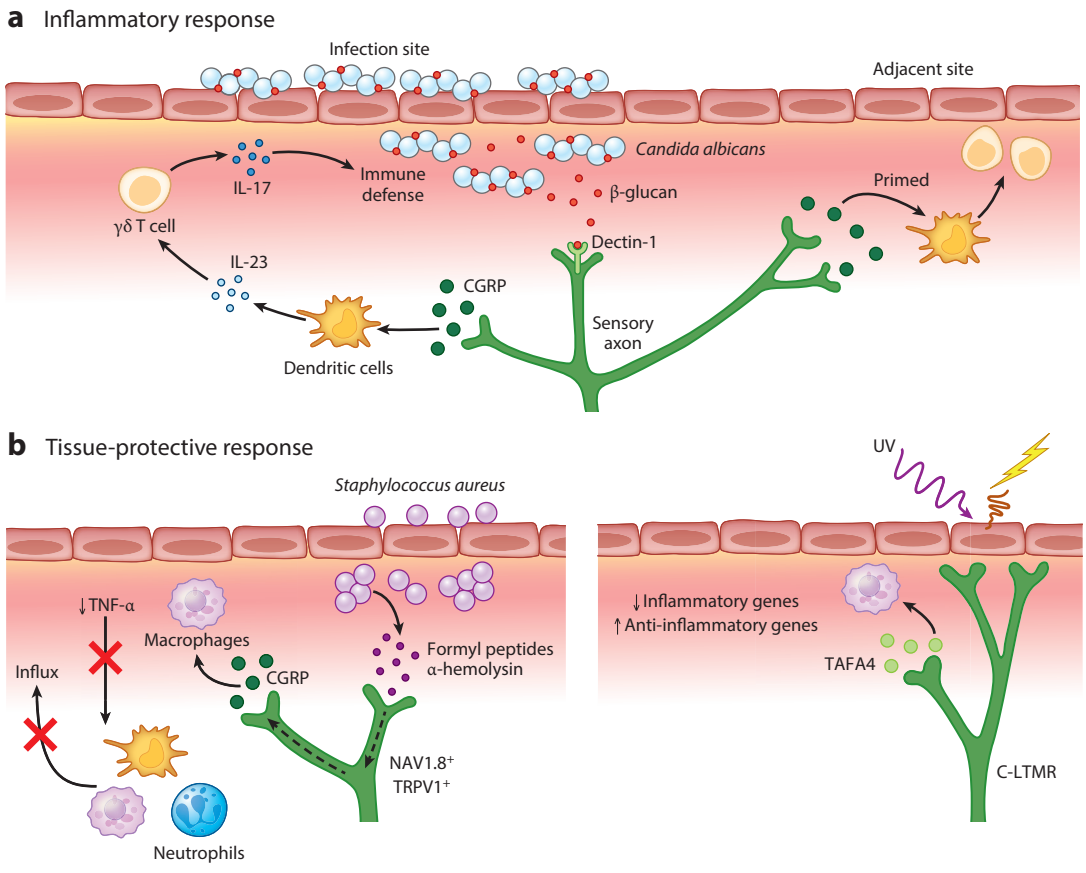


Figure 8

Sensory nerves modulate immune function in the skin. (*a*) Skin infection with *Candida albicans* induces inflammation through sensory nerves. Pathogen-secreted β-glucan binds to Dectin-1 receptors on sensory nerves. Calcitonin gene–related peptide (CGRP) released by activated sensory nerves at the site of infection elevates the expression of interleukin-23 (IL-23) by dendritic cells. IL-23 induces IL-17 production in γδ T cells, thereby activating immune responses for pathogen clearance. Activated sensory neurons also signal to immune cells at adjacent sites, priming them in case the pathogen spreads. (*b*) Subpopulations of sensory nerves regulate tissue-protective responses in immune cells. Formyl peptides and α-hemolysin from *Staphylococcus aureus* activate NAV1.8$^+$ and TRPV1$^+$ sensory neurons. Activated sensory neurons release CGRP to downregulate the expression of inflammatory signals such as tumor necrosis factor alpha (TNF-α) in macrophages, preventing monocyte influx. Ultraviolet (UV)-induced skin damage (*lightning bolt*) activates a population of C–low threshold mechanoreceptor (C-LTMR) sensory neurons that release TAFA4 to downregulate the expression of inflammatory genes and increase the expression of genes involved in tissue protection in macrophages.

damage elicits IL-17 production in γδ T cells and primes the skin to clear *C. albicans* infections faster (Cohen et al. 2019), demonstrating the importance of nociceptive neurons in mounting immune responses against pathogens.

Another example in which neurons can directly sense pathogens is in *Staphylococcus aureus* infection—one of the most common and deadly bacterial infections associated with wounds and surgery. *S. aureus*–derived N-formylated peptides and the pore-forming toxin α-hemolysin induce action potentials and calcium ion influx in NAV1.8$^+$ and TRPV1$^+$ nociceptive neurons to cause painful sensations at the site of infection. The activation of NAV1.8$^+$ and TRPV1$^+$ nociceptive

neurons by these bacterial components leads to the release of CGRP in the skin and inhibits tumor necrosis factor alpha (TNF-α) production in macrophages (**Figure 8*b***). The reduction in TNF-α suppresses monocyte influx into the skin and reduces draining lymph node hypertrophy (Chiu et al. 2013).

Besides nociceptive neurons, touch-sensing neurons also play a role in modulating skin immunity. After ultraviolet (UV) exposure, C–low threshold mechanoreceptor (C-LTMR) sensory nerves secrete a neuropeptide, TAFA4, that downregulates inflammation and prevents fibrosis after UV-induced tissue damage by modulating dermal macrophages (Hoeffel et al. 2021) (**Figure 8*b***). Although the inhibition of immune cells during infection seems counterintuitive, it is essential to prevent the detrimental consequences associated with an overactive immune system. Together, these studies suggest that sensory neurons modulate the immune response for pathogen clearance while preventing an overactivation that could damage the skin.

Some bacteria have evolved to hijack this neuroimmune circuitry. In the case of *Streptococcus pyogenes* infection—another common pathogen causing skin infections—the bacteria secrete a pore-forming toxin to activate TRPV1$^+$ nociceptive sensory neurons to induce pain. CGRP secreted from these neurons then suppresses neutrophil recruitment and prevents neutrophils from killing *S. pyogenes*. Blocking the neuroimmune communication with botulinum neurotoxin A, which prevents CGRP release, or with injection of a CGRP antagonist significantly improves the outcome of *S. pyogenes* infection (Pinho-Ribeiro et al. 2018).

Neuroimmune interactions also contribute to immune-related diseases. Psoriasis is an immune-related disorder that accelerates epidermal proliferation and causes raised, scaly skin patches. One of the most prevalent immune disorders, it affects more than 3% of the adult population in the United States alone (Armstrong et al. 2021). Patients with psoriasis often report sensations of itch and discomfort within skin lesions. Clinical studies suggest that damage to cutaneous nerves can ameliorate inflammation and skin changes in psoriasis patients, indicating a role for peripheral nerves in modulating the severity of this disease (Farber et al. 1990). In mice, topical imiquimod (IMQ) application induces γδT17-cell-mediated inflammation that resembles psoriasis. Chemical ablation of sensory neurons prevents IMQ-induced inflammation, whereas ablation of sympathetic neurons only reduces swelling but does not prevent immune cell activation and infiltration, suggesting that different peripheral nerves regulate different aspects of the immune response. Sensory nerves mediate inflammatory responses and orchestrate skin immune cell behaviors by acutely regulating IL-23 production from dermal dendritic cells (Riol-Blanco et al. 2014).

Collectively, these examples demonstrate the vital role of peripheral nerves in regulating immune cells during host defense, inflammation, and injury. Given the unique ability of the nervous system to transmit rapid responses, it is particularly suited to act as the first responder to initiate the slower immune cell cascade that then has a longer-lasting impact. This relaying mechanism is reminiscent of how the nervous system modulates hair growth in response to cold by relaying its effect to a longer-lasting signal. The widespread nature of peripheral innervation may also serve as a convenient route to prime surrounding tissues or influence distant areas, such as the bone marrow, that are far away from the infection site. This interconnection could then coordinate tissue-specific immune cells with HSC behaviors to expedite pathogen clearance and potentially help create a memory of the infection.

CONCLUSIONS

Neurobiology, stem cell biology, and immunology have traditionally been studied as three largely separate fields. In this review, we discuss studies that break these boundaries and merge these

fields. Several common themes have emerged from these synergistic studies. First, tissue regeneration and repair do not operate in isolation in individual organs. Instead, local tissue changes and immune responses are tightly integrated with bodily and environmental changes by the PNS. Second, neurons communicate with stem cells and immune cells either directly or indirectly via neurotransmitters (such as norepinephrine) and neuropeptides (such as CGRP). Although these molecules act over short distances and have short half-lives, their effect is often sustained and amplified by inducing the expression of secreted proteins (such as cytokines) in target cells. In this sense, neurons are often the activators that initiate downstream responses. Third, changes in neuronal activity and innervation density can be the root cause for a wide variety of conditions and diseases that may seem unrelated to the nervous system, including stress-related tissue deterioration and immune changes, defects in wound repair, aging, and cancer.

These findings suggest a number of avenues for future exploration. Some of these studies may focus on further delineating initial observations. For example, although neuronal inputs are critical modulators of many tissue processes, the specific class of neurons involved, as well as the cellular and molecular mechanisms by which neurons alter tissue biology and immune changes, remains to be elucidated in most cases. Other studies may continue to integrate neurobiology into our understanding of tissue homeostasis. For example, neurons can have tonic firing (steady action potential firing at a low background level that is constant or sustained over a long duration) and phasic firing (one or a few short bursts of action potentials that are substantially above background activity). Can the amplitude and duration of neuronal activity lead to different outcomes in tissue changes, and, if so, what are the mechanisms by which these types of activity are interpreted? Finally, these studies suggest new opportunities for therapeutic interventions, and future studies could aim to further develop these ideas. For example, one could explore how internal organs may be modulated by stimulating innervation at a more superficial level, such as the skin, and thereby take advantage of the elaborate wiring of the nervous system. While current medical interventions often take an organ-specific approach to treating symptoms manifested at a specific location, a better understanding of neuro–stem cell and neuroimmune interactions offers tremendous opportunities to achieve a more holistic approach for both treating and preventing diseases in the future.

DISCLOSURE STATEMENT

Y.-C.H. is one of the inventors for a patent application (PCT/US2020/024772). E.S.-S. is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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LITERATURE CITED

Abraira VE, Ginty DD. 2013. The sensory neurons of touch. *Neuron* 79:618–39

Adams SC, Schondorf R, Benoit J, Kilgour RD. 2015. Impact of cancer and chemotherapy on autonomic nervous system function and cardiovascular reactivity in young adults with cancer: a case-controlled feasibility study. *BMC Cancer* 15:414

Akinrodoye MA, Lui F. 2022. Neuroanatomy, somatic nervous system. In *StatPearls*. Treasure Island, FL: StatPearls Publ.

Alexander GM, Rogan SC, Abbas AI, Armbruster BN, Pei Y, et al. 2009. Remote control of neuronal activity in transgenic mice expressing evolved G protein-coupled receptors. *Neuron* 63:27–39

Argyriou AA, Bruna J, Marmiroli P, Cavaletti G. 2012. Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. *Crit. Rev. Oncol. Hematol.* 82:51–77

Armbruster BN, Li X, Pausch MH, Herlitze S, Roth BL. 2007. Evolving the lock to fit the key to create a family of G protein-coupled receptors potently activated by an inert ligand. *PNAS* 104:5163–68

Armstrong AW, Mehta MD, Schupp CW, Gondo GC, Bell SJ, Griffiths CEM. 2021. Psoriasis prevalence in adults in the United States. *JAMA Dermatol.* 157:940–46

Bajayo A, Bar A, Denes A, Bachar M, Kram V, et al. 2012. Skeletal parasympathetic innervation communicates central IL-1 signals regulating bone mass accrual. *PNAS* 109:15455–60

Barker N, van Es JH, Kuipers J, Kujala P, van den Born M, et al. 2007. Identification of stem cells in small intestine and colon by marker gene *Lgr5*. *Nature* 449:1003–7

Baryawno N, Przybylski D, Kowalczyk MS, Kfoury Y, Severe N, et al. 2019. A cellular taxonomy of the bone marrow stroma in homeostasis and leukemia. *Cell* 177:1915–32.e16

Basbaum AI, Bautista DM, Scherrer G, Julius D. 2009. Cellular and molecular mechanisms of pain. *Cell* 139:267–84

Bautista DM, Siemens J, Glazer JM, Tsuruda PR, Basbaum AI, et al. 2007. The menthol receptor TRPM8 is the principal detector of environmental cold. *Nature* 448:204–8

Beronja S, Livshits G, Williams S, Fuchs E. 2010. Rapid functional dissection of genetic networks via tissue-specific transduction and RNAi in mouse embryos. *Nat. Med.* 16:821–27

Biaggioni I. 2008. Circadian clocks, autonomic rhythms, and blood pressure dipping. *Hypertension* 52:797–98

Biemesderfer D, Munger BL, Binck J, Dubner R. 1978. The pilo-Ruffini complex: a non-sinus hair and associated slowly-adapting mechanoreceptor in primate facial skin. *Brain Res.* 142:197–222

Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, et al. 2000. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* 405:458–62

Botchkarev VA, Peters EM, Botchkareva NV, Maurer M, Paus R. 1999. Hair cycle-dependent changes in adrenergic skin innervation, and hair growth modulation by adrenergic drugs. *J. Invest. Dermatol.* 113:878–87

Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. 2005. Millisecond-timescale, genetically targeted optical control of neural activity. *Nat. Neurosci.* 8:1263–68

Brady RD, Wong KR, Robinson DL, Mychasiuk R, McDonald SJ, et al. 2019. Bone health in rats with temporal lobe epilepsy in the absence of anti-epileptic drugs. *Front. Pharmacol.* 10:1278

Braz JM, Nassar MA, Wood JN, Basbaum AI. 2005. Parallel "pain" pathways arise from subpopulations of primary afferent nociceptor. *Neuron* 47:787–93

Brown HE, Dougherty TF. 1956. The diurnal variation of blood leucocytes in normal and adrenalectomized mice. *Endocrinology* 58:365–75

Brownell I, Guevara E, Bai CB, Loomis CA, Joyner AL. 2011. Nerve-derived Sonic hedgehog defines a niche for hair follicle stem cells capable of becoming epidermal stem cells. *Cell Stem Cell* 8:552–65

Cavanaugh DJ, Chesler AT, Jackson AC, Sigal YM, Yamanaka H, et al. 2011. Trpv1 reporter mice reveal highly restricted brain distribution and functional expression in arteriolar smooth muscle cells. *J. Neurosci.* 31:5067–77

Chan KY, Jang MJ, Yoo BB, Greenbaum A, Ravi N, et al. 2017. Engineered AAVs for efficient noninvasive gene delivery to the central and peripheral nervous systems. *Nat. Neurosci.* 20:1172–79

Chang CY, Pasolli HA, Giannopoulou EG, Guasch G, Gronostajski RM, et al. 2013. NFIB is a governor of epithelial-melanocyte stem cell behaviour in a shared niche. *Nature* 495:98–102

Chen C-S, Barnoud C, Scheiermann C. 2021. Peripheral neurotransmitters in the immune system. *Curr. Opin. Physiol.* 19:73–79
Chiu IM, Barrett LB, Williams EK, Strochlic DE, Lee S, et al. 2014. Transcriptional profiling at whole population and single cell levels reveals somatosensory neuron molecular diversity. *eLife* 3:e04660
Chiu IM, Heesters BA, Ghasemlou N, Von Hehn CA, Zhao F, et al. 2013. Bacteria activate sensory neurons that modulate pain and inflammation. *Nature* 501:52–57
Choi S, Zhang B, Ma S, Gonzalez-Celeiro M, Stein D, et al. 2021. Corticosterone inhibits GAS6 to govern hair follicle stem-cell quiescence. *Nature* 592:428–32
Chu C, Artis D, Chiu IM. 2020. Neuro-immune interactions in the tissues. *Immunity* 52:464–74
Clausen BE, Burkhardt C, Reith W, Renkawitz R, Förster I. 1999. Conditional gene targeting in macrophages and granulocytes using LysMcre mice. *Transgenic Res.* 8:265–77
Cohen JA, Edwards TN, Liu AW, Hirai T, Jones MR, et al. 2019. Cutaneous TRPV1^{+} neurons trigger protective innate type 17 anticipatory immunity. *Cell* 178:919–32.e14
De Giorgi V, Grazzini M, Benemei S, Marchionni N, Botteri E, et al. 2018. Propranolol for off-label treatment of patients with melanoma: results from a cohort study. *JAMA Oncol.* 4:e172908-e08
de Jonge WJ, van der Zanden EP, The FO, Bijlsma MF, van Westerloo DJ, et al. 2005. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. *Nat. Immunol.* 6:844–51
Dhaka A, Earley TJ, Watson J, Patapoutian A. 2008. Visualizing cold spots: TRPM8-expressing sensory neurons and their projections. *J. Neurosci.* 28:566–75
Dong X, Han S, Zylka MJ, Simon MI, Anderson DJ. 2001. A diverse family of GPCRs expressed in specific subsets of nociceptive sensory neurons. *Cell* 106:619–32
Elefteriou F, Ahn JD, Takeda S, Starbuck M, Yang X, et al. 2005. Leptin regulation of bone resorption by the sympathetic nervous system and CART. *Nature* 434:514–20
English KB, Kavka-Van Norman D, Horch K. 1983. Effects of chronic denervation in type I cutaneous mechanoreceptors (Haarscheiben). *Anat. Rec.* 207:79–88
Fan SM-Y, Chang Y-T, Chen C-L, Wang W-H, Pan M-K, et al. 2018. External light activates hair follicle stem cells through eyes via an ipRGC–SCN–sympathetic neural pathway. *PNAS* 115:E6880–89
Farber EM, Lanigan SW, Boer J. 1990. The role of cutaneous sensory nerves in the maintenance of psoriasis. *Int. J. Dermatol.* 29:418–20
Farrell MS, Pei Y, Wan Y, Yadav PN, Daigle TL, et al. 2013. A $G\alpha_s$ DREADD mouse for selective modulation of cAMP production in striatopallidal neurons. *Neuropsychopharmacology* 38:854–62
Ferron M, Vacher J. 2005. Targeted expression of Cre recombinase in macrophages and osteoclasts in transgenic mice. *Genesis* 41:138–45
Fujiwara H, Ferreira M, Donati G, Marciano DK, Linton JM, et al. 2011. The basement membrane of hair follicle stem cells is a muscle cell niche. *Cell* 144:577–89
Furlan A, La Manno G, Lübke M, Häring M, Abdo H, et al. 2016. Visceral motor neuron diversity delineates a cellular basis for nipple- and pilo-erection muscle control. *Nat. Neurosci.* 19:1331–40
Gabanyi I, Muller PA, Feighery L, Oliveira TY, Costa-Pinto FA, Mucida D. 2016. Neuro-immune interactions drive tissue programming in intestinal macrophages. *Cell* 164:378–91
Gao X, Zhang D, Xu C, Li H, Caron KM, Frenette PS. 2021. Nociceptive nerves regulate haematopoietic stem cell mobilization. *Nature* 589:591–96
García A, Arranz L, Sánchez-Aguilera A, Airaksinen M, Méndez-Ferrer S. 2013. Circadian parasympathetic regulation of hematopoietic stem cell traffic. *Exp. Hematol.* 41:S14
García-García A, Korn C, García-Fernández M, Domingues O, Villadiego J, et al. 2019. Dual cholinergic signals regulate daily migration of hematopoietic stem cells and leukocytes. *Blood* 133:224–36
Ge Y, Miao Y, Gur-Cohen S, Gomez N, Yang H, et al. 2020. The aging skin microenvironment dictates stem cell behavior. *PNAS* 117:5339–50
Glasner A, Avraham R, Rosenne E, Benish M, Zmora O, et al. 2010. Improving survival rates in two models of spontaneous postoperative metastasis in mice by combined administration of a β-adrenergic antagonist and a cyclooxygenase-2 inhibitor. *J. Immunol.* 184:2449–57
Godinho-Silva C, Cardoso F, Veiga-Fernandes H. 2019. Neuro-immune cell units: a new paradigm in physiology. *Annu. Rev. Immunol.* 37:19–46

Grover A, Sanjuan-Pla A, Thongjuea S, Carrelha J, Giustacchini A, et al. 2016. Single-cell RNA sequencing reveals molecular and functional platelet bias of aged haematopoietic stem cells. *Nat. Commun.* 7:11075

Haas S, Trumpp A, Milsom MD. 2018. Causes and consequences of hematopoietic stem cell heterogeneity. *Cell Stem Cell* 22:627–38

Halberg F, Visscher MB, Bittner JJ. 1953. Eosinophil rhythm in mice: range of occurrence; effects of illumination, feeding, and adrenalectomy. *Am. J. Physiol.* 174:109–22

Han L, Ma C, Liu Q, Weng H-J, Cui Y, et al. 2013. A subpopulation of nociceptors specifically linked to itch. *Nat. Neurosci.* 16:174–82

Hayakawa Y, Sakitani K, Konishi M, Asfaha S, Niikura R, et al. 2017. Nerve growth factor promotes gastric tumorigenesis through aberrant cholinergic signaling. *Cancer Cell* 31:21–34

Heidt T, Sager HB, Courties G, Dutta P, Iwamoto Y, et al. 2014. Chronic variable stress activates hematopoietic stem cells. *Nat. Med.* 20:754–58

Hjerling-Leffler J, Alqatari M, Ernfors P, Koltzenburg M. 2007. Emergence of functional sensory subtypes as defined by transient receptor potential channel expression. *J. Neurosci.* 27:2435–43

Hoeffel G, Debroas G, Roger A, Rossignol R, Gouilly J, et al. 2021. Sensory neuron-derived TAFA4 promotes macrophage tissue repair functions. *Nature* 594:94–99

Hsu Y-C, Fuchs E. 2021. Building and maintaining the skin. *Cold Spring Harb. Perspect. Biol.* 14:a040840. **https://cshperspectives.cshlp.org/content/14/7/a040840.short**

Huang S, Kuri P, Aubert Y, Brewster M, Li N, et al. 2021a. Lgr6 marks epidermal stem cells with a nerve-dependent role in wound re-epithelialization. *Cell Stem Cell* 28:1582–96.e6

Huang S, Ziegler CGK, Austin J, Mannoun N, Vukovic M, et al. 2021b. Lymph nodes are innervated by a unique population of sensory neurons with immunomodulatory potential. *Cell* 184:441–59.e25

Iggo A, Muir AR. 1969. The structure and function of a slowly adapting touch corpuscle in hairy skin. *J. Physiol.* 200:763–96

Ito M, Liu Y, Yang Z, Nguyen J, Liang F, et al. 2005. Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis. *Nat. Med.* 11:1351–54

Jacobson A, Yang D, Vella M, Chiu IM. 2021. The intestinal neuro-immune axis: crosstalk between neurons, immune cells, and microbes. *Mucosal Immunol.* 14:555–65

Jenkins BA, Fontecilla NM, Lu CP, Fuchs E, Lumpkin EA. 2019. The cellular basis of mechanosensory Merkel-cell innervation during development. *eLife* 8:e42633

Joost S, Annusver K, Jacob T, Sun X, Dalessandri T, et al. 2020. The molecular anatomy of mouse skin during hair growth and rest. *Cell Stem Cell* 26:441–57.e7

Kamiya A, Hayama Y, Kato S, Shimomura A, Shimomura T, et al. 2019. Genetic manipulation of autonomic nerve fiber innervation and activity and its effect on breast cancer progression. *Nat. Neurosci.* 22:1289–305

Kanat O, Ertas H, Caner B. 2017. Platinum-induced neurotoxicity: a review of possible mechanisms. *World J. Clin. Oncol.* 8:329–35

Karemaker JM. 2017. An introduction into autonomic nervous function. *Physiol. Meas.* 38:R89–118

Kashem SW, Riedl MS, Yao C, Honda CN, Vulchanova L, Kaplan DH. 2015. Nociceptive sensory fibers drive interleukin-23 production from CD301b^{+} dermal dendritic cells and drive protective cutaneous immunity. *Immunity* 43:515–26

Katayama Y, Battista M, Kao WM, Hidalgo A, Peired AJ, et al. 2006. Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. *Cell* 124:407–21

Keyes BE, Liu S, Asare A, Naik S, Levorse J, et al. 2016. Impaired epidermal to dendritic T cell signaling slows wound repair in aged skin. *Cell* 167:1323–38.e14

Keyes BE, Segal JP, Heller E, Lien W-H, Chang C-Y, et al. 2013. Nfatc1 orchestrates aging in hair follicle stem cells. *PNAS* 110:E4950–59

Knox SM, Lombaert IM, Haddox CL, Abrams SR, Cotrim A, et al. 2013. Parasympathetic stimulation improves epithelial organ regeneration. *Nat. Commun.* 4:1494

Knox SM, Lombaert IM, Reed X, Vitale-Cross L, Gutkind JS, Hoffman MP. 2010. Parasympathetic innervation maintains epithelial progenitor cells during salivary organogenesis. *Science* 329:1645–47

Koizumi S, Fujishita K, Inoue K, Shigemoto-Mogami Y, Tsuda M, Inoue K. 2004. Ca^{2+} waves in keratinocytes are transmitted to sensory neurons: the involvement of extracellular ATP and P2Y2 receptor activation. *Biochem. J.* 380:329–38

Lerner AB. 1966. Gray hair and sympathectomy. Report of a case. *Arch. Dermatol.* 93:235–36
Li C-L, Li K-C, Wu D, Chen Y, Luo H, et al. 2016. Somatosensory neuron types identified by high-coverage single-cell RNA-sequencing and functional heterogeneity. *Cell Res.* 26:83–102
Li L, Rutlin M, Abraira VE, Cassidy C, Kus L, et al. 2011. The functional organization of cutaneous low-threshold mechanosensory neurons. *Cell* 147:1615–27
Lin EE, Scott-Solomon E, Kuruvilla R. 2021. Peripheral innervation in the regulation of glucose homeostasis. *Trends Neurosci.* 44:189–202
Liu Q, Vrontou S, Rice FL, Zylka MJ, Dong X, Anderson DJ. 2007. Molecular genetic visualization of a rare subset of unmyelinated sensory neurons that may detect gentle touch. *Nat. Neurosci.* 10:946–48
Liu S, Wang Z, Su Y, Qi L, Yang W, et al. 2021. A neuroanatomical basis for electroacupuncture to drive the vagal-adrenal axis. *Nature* 598:641–45
Liu S, Wang Z-F, Su Y-S, Ray RS, Jing X-H, et al. 2020. Somatotopic organization and intensity dependence in driving distinct NPY-expressing sympathetic pathways by electroacupuncture. *Neuron* 108:436–50.e7
Lu W-J, Mann RK, Nguyen A, Bi T, Silverstein M, et al. 2018. Neuronal delivery of Hedgehog directs spatial patterning of taste organ regeneration. *PNAS* 115:E200–9
Lu Z, Xie Y, Huang H, Jiang K, Zhou B, et al. 2020. Hair follicle stem cells regulate retinoid metabolism to maintain the self-renewal niche for melanocyte stem cells. *eLife* 9:e52712
Lucas D, Battista M, Shi PA, Isola L, Frenette PS. 2008. Mobilized hematopoietic stem cell yield depends on species-specific circadian timing. *Cell Stem Cell* 3:364–66
Lucas D, Scheiermann C, Chow A, Kunisaki Y, Bruns I, et al. 2013. Chemotherapy-induced bone marrow nerve injury impairs hematopoietic regeneration. *Nat. Med.* 19:695–703
Luiz AP, MacDonald DI, Santana-Varela S, Millet Q, Sikandar S, et al. 2019. Cold sensing by $Na_V1.8$-positive and $Na_V1.8$-negative sensory neurons. *PNAS* 116:3811–16
Lumpkin EA, Caterina MJ. 2007. Mechanisms of sensory transduction in the skin. *Nature* 445:858–65
Ma Q. 2020. Somato-autonomic reflexes of acupuncture. *Med. Acupunct.* 32:362–66
Ma S, Zhang B, LaFave LM, Earl AS, Chiang Z, et al. 2020. Chromatin potential identified by shared single-cell profiling of RNA and chromatin. *Cell* 183:1103–16.e20
Mach DB, Rogers SD, Sabino MC, Luger NM, Schwei MJ, et al. 2002. Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. *Neuroscience* 113:155–66
Madeo M, Colbert PL, Vermeer DW, Lucido CT, Cain JT, et al. 2018. Cancer exosomes induce tumor innervation. *Nat. Commun.* 9:4284
Magnon C, Hall SJ, Lin J, Xue X, Gerber L, et al. 2013. Autonomic nerve development contributes to prostate cancer progression. *Science* 341:1236361
Maruyama K, Takayama Y, Sugisawa E, Yamanoi Y, Yokawa T, et al. 2018. The ATP transporter VNUT mediates induction of dectin-1-triggered *Candida* nociception. *iScience* 6:306–18
Maryanovich M, Zahalka AH, Pierce H, Pinho S, Nakahara F, et al. 2018. Adrenergic nerve degeneration in bone marrow drives aging of the hematopoietic stem cell niche. *Nat. Med.* 24:782–91
Massberg S, Schaerli P, Knezevic-Maramica I, Köllnberger M, Tubo N, et al. 2007. Immunosurveillance by hematopoietic progenitor cells trafficking through blood, lymph, and peripheral tissues. *Cell* 131:994–1008
Matheis F, Muller PA, Graves CL, Gabanyi I, Kerner ZJ, et al. 2020. Adrenergic signaling in muscularis macrophages limits infection-induced neuronal loss. *Cell* 180:64–78.e16
Matteoli G, Gomez-Pinilla PJ, Nemethova A, Di Giovangiulio M, Cailotto C, et al. 2014. A distinct vagal anti-inflammatory pathway modulates intestinal muscularis resident macrophages independent of the spleen. *Gut* 63:938–48
Mattiuz R, Wohn C, Ghilas S, Ambrosini M, Alexandre YO, et al. 2018. Novel Cre-expressing mouse strains permitting to selectively track and edit type 1 conventional dendritic cells facilitate disentangling their complexity *in vivo*. *Front. Immunol.* 9:2805
McKim DB, Patterson JM, Wohleb ES, Jarrett BL, Reader BF, et al. 2016. Sympathetic release of splenic monocytes promotes recurring anxiety following repeated social defeat. *Biol. Psychiatry* 79:803–13
McNees P, Meneses KD. 2007. Pressure ulcers and other chronic wounds in patients with and patients without cancer: a retrospective, comparative analysis of healing patterns. *Ostomy Wound Manag.* 53:70–78

Melton LJ 3rd, Beard CM, Kokmen E, Atkinson EJ, O'Fallon WM. 1994. Fracture risk in patients with Alzheimer's disease. *J. Am. Geriatr. Soc.* 42:614–19

Méndez-Ferrer S, Battista M, Frenette PS. 2010. Cooperation of β_2- and β_3-adrenergic receptors in hematopoietic progenitor cell mobilization. *Ann. N.Y. Acad. Sci.* 1192:139–44

Méndez-Ferrer S, Lucas D, Battista M, Frenette PS. 2008. Haematopoietic stem cell release is regulated by circadian oscillations. *Nature* 452:442–47

Meregnani J, Clarençon D, Vivier M, Peinnequin A, Mouret C, et al. 2011. Anti-inflammatory effect of vagus nerve stimulation in a rat model of inflammatory bowel disease. *Auton. Neurosci.* 160:82–89

Moen SM, Celius EG, Sandvik L, Nordsletten L, Eriksen EF, Holmøy T. 2011. Low bone mass in newly diagnosed multiple sclerosis and clinically isolated syndrome. *Neurology* 77:151–57

Morrison KM, Miesegaes GR, Lumpkin EA, Maricich SM. 2009. Mammalian Merkel cells are descended from the epidermal lineage. *Dev. Biol.* 336:76–83

Nakai A, Hayano Y, Furuta F, Noda M, Suzuki K. 2014. Control of lymphocyte egress from lymph nodes through β_2-adrenergic receptors. *J. Exp. Med.* 211:2583–98

Nguyen MB, Cohen I, Kumar V, Xu Z, Bar C, et al. 2018. FGF signalling controls the specification of hair placode-derived SOX9 positive progenitors to Merkel cells. *Nat. Commun.* 9:2333

Olson OC, Kang Y-A, Passegué E. 2020. Normal hematopoiesis is a balancing act of self-renewal and regeneration. *Cold Spring Harb. Perspect. Med.* 10:a035519

Ordovas-Montanes J, Rakoff-Nahoum S, Huang S, Riol-Blanco L, Barreiro O, von Andrian UH. 2015. The regulation of immunological processes by peripheral neurons in homeostasis and disease. *Trends Immunol.* 36:578–604

Ortonne JP, Thivolet J, Guillet R. 1982. Graying of hair with age and sympathectomy. *Arch. Dermatol.* 118:876–77

Pan Y, Hysinger JD, Barron T, Schindler NF, Cobb O, et al. 2021. NF1 mutation drives neuronal activity-dependent initiation of optic glioma. *Nature* 594:277–82

Patel A, Yamashita N, Ascaño M, Bodmer D, Boehm E, et al. 2015. RCAN1 links impaired neurotrophin trafficking to aberrant development of the sympathetic nervous system in Down syndrome. *Nat. Commun.* 6:10119

Perdigoto CN, Dauber KL, Bar C, Tsai P-C, Valdes VJ, et al. 2016. Polycomb-mediated repression and Sonic hedgehog signaling interact to regulate Merkel cell specification during skin development. *PLOS Genet.* 12:e1006151

Peterson SC, Eberl M, Vagnozzi AN, Belkadi A, Veniaminova NA, et al. 2015. Basal cell carcinoma preferentially arises from stem cells within hair follicle and mechanosensory niches. *Cell Stem Cell* 16:400–12

Pinho-Ribeiro FA, Baddal B, Haarsma R, O'Seaghdha M, Yang NJ, et al. 2018. Blocking neuronal signaling to immune cells treats streptococcal invasive infection. *Cell* 173:1083–97.e22

Powell ND, Sloan EK, Bailey MT, Arevalo JM, Miller GE, et al. 2013. Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via β-adrenergic induction of myelopoiesis. *PNAS* 110:16574–79

Rabbani P, Takeo M, Chou W, Myung P, Bosenberg M, et al. 2011. Coordinated activation of Wnt in epithelial and melanocyte stem cells initiates pigmented hair regeneration. *Cell* 145:941–55

Rabben H-L, Zhao C-M, Hayakawa Y, Wang TC, Chen D. 2016. Vagotomy and gastric tumorigenesis. *Curr. Neuropharmacol.* 14:967–72

Rachmin I, Lee JH, Zhang B, Sefton J, Jung I, et al. 2021. Stress-associated ectopic differentiation of melanocyte stem cells and ORS amelanotic melanocytes in an ex vivo human hair follicle model. *Exp. Dermatol.* 30:578–87

Riol-Blanco L, Ordovas-Montanes J, Perro M, Naval E, Thiriot A, et al. 2014. Nociceptive sensory neurons drive interleukin-23-mediated psoriasiform skin inflammation. *Nature* 510:157–61

Scheiermann C, Kunisaki Y, Lucas D, Chow A, Jang JE, et al. 2012. Adrenergic nerves govern circadian leukocyte recruitment to tissues. *Immunity* 37:290–301

Scott-Solomon E, Boehm E, Kuruvilla R. 2021. The sympathetic nervous system in development and disease. *Nat. Rev. Neurosci.* 22:685–702

Seifert P, Spitznas M. 2002. Axons in human choroidal melanoma suggest the participation of nerves in the control of these tumors. *Am. J. Ophthalmol.* 133:711–13

Shukla PK, Meena AS, Dalal K, Canelas C, Samak G, et al. 2021. Chronic stress and corticosterone exacerbate alcohol-induced tissue injury in the gut-liver-brain axis. *Sci. Rep.* 11:826
Shwartz Y, Gonzalez-Celeiro M, Chen C-L, Pasolli HA, Sheu S-H, et al. 2020. Cell types promoting goosebumps form a niche to regulate hair follicle stem cells. *Cell* 182:578–93.e19
Sipe LM, Yang C, Ephrem J, Garren E, Hirsh J, Deppmann CD. 2017. Differential sympathetic outflow to adipose depots is required for visceral fat loss in response to calorie restriction. *Nutr. Diabetes* 7:e260
Sivamani RK, Pullar CE, Manabat-Hidalgo CG, Rocke DM, Carlsen RC, et al. 2009. Stress-mediated increases in systemic and local epinephrine impair skin wound healing: potential new indication for beta blockers. *PLOS Med.* 6:e1000012
Somers VK, Dyken ME, Mark AL, Abboud FM. 1993. Sympathetic-nerve activity during sleep in normal subjects. *N. Engl. J. Med.* 328:303–7
Song H, Fang F, Tomasson G, Arnberg FK, Mataix-Cols D, et al. 2018. Association of stress-related disorders with subsequent autoimmune disease. *JAMA* 319:2388–400
Stachniak TJ, Ghosh A, Sternson SM. 2014. Chemogenetic synaptic silencing of neural circuits localizes a hypothalamus→midbrain pathway for feeding behavior. *Neuron* 82:797–808
Stickels RR, Murray E, Kumar P, Li J, Marshall JL, et al. 2021. Highly sensitive spatial transcriptomics at near-cellular resolution with Slide-seqV2. *Nat. Biotechnol.* 39:313–19
Stirling LC, Forlani G, Baker MD, Wood JN, Matthews EA, et al. 2005. Nociceptor-specific gene deletion using heterozygous $Na_V1.8$-Cre recombinase mice. *Pain* 113:27–36
Story GM, Peier AM, Reeve AJ, Eid SR, Mosbacher J, et al. 2003. ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. *Cell* 112:819–29
Tam J, Trembovler V, Di Marzo V, Petrosino S, Leo G, et al. 2008. The cannabinoid CB1 receptor regulates bone formation by modulating adrenergic signaling. *FASEB J.* 22:285–94
Tanay A, Regev A. 2017. Scaling single-cell genomics from phenomenology to mechanism. *Nature* 541:331–38
Tikhonova AN, Dolgalev I, Hu H, Sivaraj KK, Hoxha E, et al. 2019. The bone marrow microenvironment at single-cell resolution. *Nature* 569:222–28
Trier AM, Mack MR, Kim BS. 2019. The neuroimmune axis in skin sensation, inflammation, and immunity. *J. Immunol.* 202:2829–35
Udit S, Blake K, Chiu IM. 2022. Somatosensory and autonomic neuronal regulation of the immune response. *Nat. Rev. Neurosci.* 23:157–71. **https://doi.org/10.1038/s41583-021-00555-4**
Usoskin D, Furlan A, Islam S, Abdo H, Lönnerberg P, et al. 2015. Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing. *Nat. Neurosci.* 18:145–53
Van Keymeulen A, Mascre G, Youseff KK, Harel I, Michaux C, et al. 2009. Epidermal progenitors give rise to Merkel cells during embryonic development and adult homeostasis. *J. Cell Biol.* 187:91–100
Veiga-Fernandes H, Mucida D. 2016. Neuro-immune interactions at barrier surfaces. *Cell* 165:801–11
Venkatesh HS, Tam LT, Woo PJ, Lennon J, Nagaraja S, et al. 2017. Targeting neuronal activity-regulated neuroligin-3 dependency in high-grade glioma. *Nature* 549:533–37
Volmer-Thole M, Lobmann R. 2016. Neuropathy and diabetic foot syndrome. *Int. J. Mol. Sci.* 17:917
Vrontou S, Wong AM, Rau KK, Koerber HR, Anderson DJ. 2013. Genetic identification of C fibres that detect massage-like stroking of hairy skin *in vivo*. *Nature* 493:669–73
Wang LD, Wagers AJ. 2011. Dynamic niches in the origination and differentiation of haematopoietic stem cells. *Nat. Rev. Mol. Cell Biol.* 12:643–55
Wu H, Williams J, Nathans J. 2012. Morphologic diversity of cutaneous sensory afferents revealed by genetically directed sparse labeling. *eLife* 1:e00181
Xiao Y, Thoresen DT, Miao L, Williams JS, Wang C, et al. 2016. A cascade of Wnt, Eda, and Shh signaling is essential for touch dome Merkel cell development. *PLOS Genet.* 12:e1006150
Xiao Y, Thoresen DT, Williams JS, Wang C, Perna J, et al. 2015. Neural Hedgehog signaling maintains stem cell renewal in the sensory touch dome epithelium. *PNAS* 112:7195–200
Yirmiya R, Goshen I, Bajayo A, Kreisel T, Feldman S, et al. 2006. Depression induces bone loss through stimulation of the sympathetic nervous system. *PNAS* 103:16876–81
Zeng X, Ye M, Resch JM, Jedrychowski MP, Hu B, et al. 2019. Innervation of thermogenic adipose tissue via a calsyntenin 3β–S100b axis. *Nature* 569:229–35

Zhang B, Hsu Y-C. 2017. Emerging roles of transit – amplifying cells in tissue regeneration and cancer. *Wiley Interdiscip. Rev. Dev. Biol.* 6:wdev.282

Zhang B, Ma S, Rachmin I, He M, Baral P, et al. 2020. Hyperactivation of sympathetic nerves drives depletion of melanocyte stem cells. *Nature* 577:676–81

Zhao Z-D, Yang WZ, Gao C, Fu X, Zhang W, et al. 2017. A hypothalamic circuit that controls body temperature. *PNAS* 114:2042–47

Zhou R, Deng J, Zhang M, Zhou H-D, Wang Y-J. 2011. Association between bone mineral density and the risk of Alzheimer's disease. *J. Alzheimer's Dis.* 24:101–8

Zhou R, Zhou H, Rui L, Xu J. 2014. Bone loss and osteoporosis are associated with conversion from mild cognitive impairment to Alzheimer's disease. *Curr. Alzheimer Res.* 11:706–13

Zylka MJ, Rice FL, Anderson DJ. 2005. Topographically distinct epidermal nociceptive circuits revealed by axonal tracers targeted to Mrgprd. *Neuron* 45:17–25