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Review Article

Reciprocal signals between nerve and epithelium: how do neurons talk with epithelial cells?

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Abstract: Most epithelium tissues continuously undergo self-renewal through proliferation and differentiation of epithelial stem cells (known as homeostasis), within a specialized stem cell niche. In highly innervated epithelium, peripheral nerves compose perineural niche and support stem cell homeostasis by releasing a variety of neurotransmitters, hormones, and growth factors and supplying trophic factors to the stem cells. Emerging evidence has shown that both sensory and motor nerves can regulate the fate of epithelial stem cells, thus influencing epithelium homeostasis. Understanding the mechanism of crosstalk between epithelial stem cells and neurons will reveal the important role of the perineural niche in physiological and pathological conditions. Herein, we review recent discoveries of the perineural niche in epithelium mainly in tissue homeostasis, with a limited touch in wound repair and pathogenesis.

Keywords: Perineural niche, tissue maintenance, stem cell, crosstalk, neurotransmitter

The perineural niche of stem cell

Most epithelial tissues, like skin and the gastrointestinal tract, undergo a continuous replacement of damaged or dead cells, known as tissue homeostasis. This process is crucial for the maintenance of adult tissues [1, 2]. Epithelial tissue homeostasis requires epithelial stem cells, which are functionally characterized by their capability to self-renew and differentiate into the cell lineages as needed [3]. Adult stem cells also play a vital role in regenerating damaged tissue after injury, which may respond to dysregulated signals from mutated cells such as cancer cells and behave abnormally [4]. Notably, stem cells exhibit incredible plasticity when local and systemic conditions vary [5, 6]. Adult stem cells reside within a specific microenvironment, known as a stem cell niche. The stem cell niche regulates the self-renewal of stem cells and prevents their precocious differentiation by regulating the secretion of growth factors and cytokines from stem cells themselves or surrounding niche cells. By using cell adhesion molecules and the extracellular matrix, stem cells keep undifferentiated and reside in place [7-12]. Given that almost all body tissues are innervated by endings of peripheral nerves, nerves make synapse-like associations or bypass through stem cells in these tissues. Factors and neurotransmitters derived from nerves have been shown to activate and promote mitosis or differentiation of stem cells [13, 14], the perineural signals are emerging as

essential factors for the renewal and long-term maintenance of stem cells, regarding as perineural niche.

The perineural niche is composed of the endings of nerves, which usually function through electrical and neurotransmitter signaling under physiological condition. Sensory nerves convert specific external and internal stimuli into electrochemical signals and carry the resulting nerve impulse to the central nervous system (CNS). Sensory receptors can be membrane-bound gated receptors of a sensory nerve, such as the olfactory receptor or they can be specialized cells, such as cutaneous Merkel cells or taste receptor cells, which are innervated by sensory nerves [15-17]. Receptor cells usually make synapse-like associations with enlarged nerve terminals [18]. Motor nerves, which are divided into somatic and autonomic (or visceral) motor nerves, relay stimuli from the CNS to peripheral effectors. Somatic motor nerves project axons into skeletal muscle while autonomic motor nerves project axons into visceral muscle and some glands. Transmitters from autonomic nerves are released at various distances from their effector cells, resulting in a widespread diffusion of signals in a paracrine secretion pattern [19]. Other than their physiological roles, the reciprocal signal communication between nerves and innervated cells is a critical component in the maintenance of the stem cell microenvironment.

Peripheral nerves have been shown to support tissue development, repair, and regeneration in lower organisms [20], and are emerging as key players in the perineural niche for mammalian stem cells now. Norepinephrine (NE) and acetylcholine (Ach) are classic neurotransmitters for sympathetic neurons and parasympathetic neurons, respectively. Evidence has shown that NE from nerves can reduce the number of hepatic progenitor cells [21], while Ach signaling stimulates the accumulation of hepatic progenitor cells [22]. Loss of sympathetic nerves in bone marrow leads to premature aging-like changes in hematopoietic stem cells, resulting in poor bone marrow repopulating activity, myeloid bias, and polarity defects [23]. On the other hand, signals from non-nerve cells control the innervated nerve's growth. Brown adipose tissue thermogenesis requires innervation by the sympathetic neurons. Meanwhile, calsyntenin 3β in adipocytes facilitates functional sympathetic innervation [24]. In injured liver, the reconstruction of nerve network depends on the NGF signaling from intrahepatic bile ducts [25]. Moreover, interaction between nerves and adult stem cells has been found to greatly enhance the wound healing response following corneal and lung injury [26, 27]. Notably, signals from nerves are also involved in many diseases, like tumorigenesis in the stomach, pancreas, prostate, intestine, and in the polycystic ovary syndrome [28, 29]. Thus, there is reciprocal signal communication between innervated tissues and the nerves.

Although the perineural niche has attracted researchers' attention, the mechanisms of how the perineural niche functions in regulating stem cells remain largely unclear. Herein, we summarize recent research investigating the reciprocal signals between neurons and epithelial cells in highly innervated epithelium tissues, including hair follicle, touch dome, taste bud, and gastrointestinal epithelia. We also discuss the mechanism underlying the crosstalk between the epithelial cell and neuronal cell in response to injury and in cancer in a less.

Crosstalk between nerve and epithelium

Hair follicle

The hair follicle (HF) is a complicated mini-organ divided into infundibulum, isthmus, bulge and hair bulb. Its epithelium is consisted of the outer root sheath (ORS) and inner root sheath (IRS). Postnatal HFs undergo spontaneous cycles of regeneration through growth (anagen), regression (catagen), and rest (telogen) status. HF stem cells (HFSCs) are essential for hair cycle. Multiple stem cell populations have been identified in the mouse telogen HF bulge and in the proliferative ORS during the anagen phase using the genetic biomarkers including K15, Lgr5, Lgr6, Sox9, CD34, Blimp1, Lrig1, Plet1, and Gli1 [30]. These stem cells provide the necessary number and type of specialized cells that take part in the hair cycle, with precise regulation by various factors, including those from the perineural niche. HFs are innervated at the bulb and bulge including somatic sensory afferents and autonomic sympathetic nerves [31]. Sensory nerves not only feel the movement of hair [32], but support the Gli1-expressing upper bulge ($Gli1^+$) HFSCs as a peri-

neural niche, participate in hair follicle growth when another anagen phase is initiated [33]. While autonomic nerves have also been evidenced to regulate HFSCs homeostasis in adult.

HFSCs are not only involved in hair follicle homeostasis but also play a vital role in skin regeneration and wound repair [34, 35]. $Gli1^+$ HFSCs function as multipotent stem cells to repeatedly regenerate HFs when these bulge cells reside in their native perineural niche that release Sonic Hedgehog (SHH). With the support of the perineural niche, these stem cells migrate into skin wounds, help healing, transform into interfollicular epidermal stem cells ($Gli1^+$ $K15^-$), and differentiate into epidermal keratinocytes. However, those epidermal stem cells cannot be maintained without the perineural niche [33]. Although dispensable for follicle contributions to acute wound healing and skin homeostasis, the sensory nerves are necessary to maintain bulge cells capable of becoming epidermal stem cells. Innervated upper bulge $Gli1^+$ cells may constitute to a long-term stem cell depository, which can replenish the epidermis after injury. This study provides evidence that stem cells are sustained in the perineural niche. Additionally, the stem cells' dependency on progeny provides a natural means for stem cells guiding them during normal homeostasis, when to start and expand tissue growth and when to stop. Moreover, when the regulatory progenitors are damaged upon wounding, the niche environment is also changed, enabling stem cells taking immediate actions accordingly to repair tissues.

Through crosstalk with neurons, HFSCs can be activated in response to external environmental changes. External light can activate HFSCs through intrinsically photosensitive retinal ganglion cells, which send signals to the suprachiasmatic nucleus of the hypothalamus. The suprachiasmatic nucleus stimulates release of NE from sympathetic neurons to activate HFSCs [36]. Another study also demonstrated that cold-induced burst-release of NE from sympathetic nerves through synapse-like structure can accelerate HFSC activation to produce new hair coat, coupling tissue growth with environmental changes [13]. On the other hand, SHH derived from HFSC progeny regulates arrector pili muscle formation and consequently maintains innervation. Since the activation of sympathetic nerves is not exclusive to HFs, it is noteworthy that such rapid adaptive responses may also happen in other homeostatic tissues.

In addition, studies have shown that chronic and sustained exposure to stress can significantly affect the hair follicle homeostasis via perineural niche [37, 38]. Acute stress causes melanocyte stem cell (MeSC) loss and premature hair greying in mice, the depletion of MeSCs during acute stress is induced by hyperactivation of sympathetic nerves that innervate MeSC niche, rather than adrenal stress hormones or immune attack [39]. The burst release of NE from sympathetic nerves leads to rapid proliferation of quiescent melanocyte stem cells followed by their differentiation, migration, and permanent loss from the niche [39]. Stress-induced hair greying is prevented by transient suppression of the proliferation of melanocyte stem cells. These findings suggest the mechanism that systematic factor can regulate a stem cell population through the perineural niche. However, it is still unclear that while stress is overcome, if the hair can turn back to black and the underlying mechanism.

Although there is little research assessing the reciprocal effect of stem cells on neurons, RNAseq analysis of mRNA expression profile of $Gli1^+$ stem cells from adult telogen mice provides some clues. Genes highly expressed by $Gli1^+$ stem cells include the ones involved in neuron differentiation (Duoxa1, Nbl1, Neurod2, Timp2, and Tcf12, etc.), neuron projection development (Snapin, Dguok, Dab2, and Lgals1, etc.), nervous system development (Lhx2, Smarca2, Nrn1, Nbl1, Neurod2, Nrbp2, Sema3e, and Tcf12, etc.), and synapse maturation (Neurod2 and Nfatc4) [33]. It implies that resident stem cells may have an important role in attracting and supporting neuron projections.

Touch dome

The touch dome (TD) is a highly innervated specialized skin appendage. It is a specific epidermal sensory structure consisting of K8-expressing Merkel cells (MCs) assembled amongst columnar basal keratinocytes that express K17. MCs and the peripheral sensory nerves form the MC-neurite complex through synaptic contact [40]. They are of particular

importance as the receptor of touch sensation [41]. Lineage tracing analysis has indicated that the entire pool of mature MCs is refreshed in the adult epidermis every 7-8 weeks [42], and new MCs regenerate after injury [43], indicating the existence of stem cells that maintain the TD epithelium. MCs and the TD originate from $K14^+$ epidermal stem cells [44, 45], and resident $Gli1^+$ or $K17^+$ stem cells also maintain the TD as a distinct epidermal lineage [42, 46-48]. Study has shown that denervation of subcutaneous nerves from the dorsal root ganglion (DRG) leads to the gradual loss of MCs and TDs [46], which might be due to waning trophic support from the DRG [48], suggesting that the perineural niche is critical for supporting the maintenance of the TD and its MCs.

During embryonic development, skin appendage forming, including TDs, depends upon the extrinsic chemokines of BMPs, WNT, and SHH, mainly from the mesenchyme [49]; while at birth, when mature MC-neurite complexes form, signals from nerve endings, such as SHH, become essential for TD maintenance [46], indicating a niche switch before and after birth for supporting TDs. Conditional knockout of the *Shh* gene in DRGs results in the disappearance of TDs and MCs and the gradual loss of $Gli1^+$ stem cells, which demonstrates that nerve-derived SHH plays a key role in the self-renewal of TD stem cells. Interestingly, the presynaptic molecular signature is enriched in MCs, suggesting that synaptic signaling may also participate in the communication between nerve and MCs [50]. So far, few nerve-derived molecules that regulate TD stem cells are identified. Because isolation of the small number of TD stem cells is a technical challenge, cutting-edge techniques, such as single-cell RNA-Seq would help to reveal more information on the interplay between TD stem cell and perineural niche. Nevertheless, new findings are expected in the field of touch biology, such as the cellular basis of how sensations are initiated. Moreover, touch and pain are closely related, thus the characterization of the underlying cellular mechanisms of touch sensation would help better understand the pain as well.

Noteworthy, nerve endings projected to TD and MC undergo pruning and maturation during both prenatal and postnatal period [51, 52]. Two molecularly distinct populations of neurons with Ret^+ and $NFH^+/TrkC^+$ sensory nerves in embryonic DRGs innervate MCs and TDs, whereas only $TrkC^+$ sensory nerve innervation persists in adult TD [53]. Selective genetic ablation of $K17^+$ TD keratinocytes suggests that $K17^+$ TD, but not mature MCs, are mainly responsible for sustaining the innervation of the MC-neurite complex [42, 54]. It has been anticipated that neural cell adhesion molecules expressed on keratinocytes in the TD may facilitate MC innervation to maintain this perineural niche [55]. Additional mechanisms are remained to be discovered for the innervation of the TD, that is important to study the MC-neurite complex, TD homeostasis, and the pathogenesis of diseases with abnormal touch sensation. Moreover, it is not completely understood how skin cells feel fine details and texture and distinguish itch and pain, especially in aging skin. Understanding the regulation of TD homeostasis would help to understand how certain diseases and aging influence the ability to sense of touch, which in turn would lead to develop new approaches for restoring the sense of touch.

Taste bud

Taste buds are specialized structures residing in the taste papillae of the tongue and are components of the sensory epithelium. Taste buds contain a variety of highly innervated taste receptor cells (TRCs), which undergo regular self-renewal under normal homeostatic conditions or upon injury [56, 57]. Fate mapping and genetic studies have identified *Shh*-expressing basal cells as the general precursors of all taste bud cell types [58]. SHH-responding cells (including $Gli1^+$, $Gli2^+$, $Ptch1^+$, Smo^+) are identified as progenitors for taste buds and are critical for taste bud functional homeostasis and injury recovery, within the support of a perineural niche [59-62].

Taste buds are innervated by the trigeminal, geniculate, and distal (petrosal) cranial nerve ganglia, whose axons transmit taste information from peripheral taste buds to the hindbrain [63]. The taste organs (taste papillae and their resident taste buds) of the anterior tongue and soft palate are innervated by visceral sensory neurons (for taste) situated in the genicular ganglion, and by somatic sensory neurons (for touch and pain) in the trigeminal ganglion [64].

The circumvallate papillae are innervated by visceral sensory neurons in the petrosal ganglion of the glossopharyngeal nerve, whereas the somatosensory neurons, projecting into the same papillae, are presumably situated in the proximal (superior) ganglion [65]. The role of neuronal innervation in the maintenance of the rabbit taste system was described 140 years ago, demonstrating that the transection of innervating sensory projections could lead to the degeneration of taste buds [66]. Denervation during perinatal development or in young postnatal rats will permanently impair the capacity of the gustatory epithelium to form taste buds and taste bud maturation [67]. In adult mammals, innervation is necessary for taste bud maintenance and differentiation. In the anterior tongue, unilateral transection of the chord-lingual nerve leads to the degeneration of taste buds and the outgrowth of the filiform spine [68]. In the vallate papilla of rat, unilateral nerve destruction leads to less taste buds [69]. In human, the damage of the chorda tympani and the glossopharyngeal nerves in patients undergoing oral surgery or surgery for chronic otitis media result in impaired taste sensitivity [70-74]. All of these suggest an essential niche composed by the peripheral nerves for the appropriate function of taste bud stem cells. Although the function of nerves in taste bud maintenance and regeneration has been described, the molecular mechanisms underlying nerve-stem cell interactions are not fully identified.

In human, the loss of TRCs also occurs when the Hh pathway is pharmacologically blocked, accounting for the loss of taste experienced by cancer patients [75-77]. These observations are consistent with the findings that loss of TRCs is associated with the blockade of the Hh pathway in mice [78-80]. Another study demonstrates that SHH is not restricted in taste buds but is also expressed in sensory neurons. Experimental ablation of neuronal derived SHH causes a loss of TRCs [81], and regeneration of stable TRCs requires neuronal SHH to ensure functional integrity, demonstrating that SHH signals from nerves can induce distal cellular responses. Thus, these findings provide an explanation of the loss of taste in cancer patients treated with Hh pathway antagonists. The local use of Hh pathway agonists may be used to accelerate the recovery of taste sensation after radiotherapy or chemotherapy. On the other hand, neurotrophic brain-derived neurotrophic factor (BDNF) secreted by taste bud cells is an essential supporting factor for taste buds innervation, as removing BDNF leads to the loss of innervation of taste buds, and overexpressing BDNF produces distinct gustatory axon morphologies that disrupt initial innervation of taste buds [81, 82]. Together, these results suggest that crosstalk between epithelial cells and nerves are required to maintain integrity of structure and functions of taste buds. This crosstalk is very crucial as the peripheral neurons form close relationship with epithelia, and transmit the signals of environmental stimulation to the brain.

Gastrointestinal epithelium

The gastrointestinal epithelium is a single layer of columnar cells that are organized into glands and pits in the stomach, crypts and villi in the intestine [83]. The epithelial cells consist of various functional cell types, which are generated from one or more stem cells located in the base or the isthmus of both gastric glands and intestinal crypts. The homeostasis of the gastrointestinal epithelium is driven by active $Lgr5^+$ stem cells at the gland and crypt bases [84, 85]. Besides $Lgr5^+$ cells, the gastrointestinal tract harbors several other stem cell populations that are activated upon epithelial injury. $Bmi1^+$ cells localize approximately four cell positions from the crypt base and $Troy^+$ derived chief cells localize at the bottom of the gastric corpus glands [86, 87]. These stem cells play a vital role in the maintenance of the gastrointestinal epithelium and rapid cell renewal in response to injury. Hence, to understand how the stem cells participate in pathological recovery, such as injury and cancer, it is important to first dissect the stem cell behavior under physiological conditions.

Unlike other tissues, the motility and secretion in the gastrointestinal tract is controlled by two nerve systems: the extrinsic sympathetic and parasympathetic nerves and the intrinsic enteric nervous system (ENS) [88]. The ENS is composed of neurons and enteric glial cells (EGCs) that are interconnected to form two ganglionated plexuses-the myenteric and the submucosal plexuses. The myenteric plexus forms a continuous network extending from the esophagus

to the internal anal sphincter while the submucosal plexus is present in the small and large intestines. Because there are intact neuronal circuits within the intestine, the function of the intestine can be controlled independent of the CNS, and the stomach is primarily controlled by extrinsic nerves.

Within the stomach, nerve fibers form a dense network that also encompasses gastric glands [89, 90], building a paracrine communication between epithelial cells and neurons. Neuronal Ach stimulates epithelial stem cell division via the muscarinic receptor-3 (M3R) that is expressed in $Lgr5^+$ cells. Co-culture with neuronal Ach-secreting neurons promotes the growth of normal gastric organoids, but not M3R-deficient gastric organoids [91]. Loss of epithelial M3R expression in mice results in decreased epithelial stem cell proliferation upon injury [92]. In gastric cancer, Ach induces the secretion of nerve growth factor (NGF) from epithelial cells, and NGF facilitates the growth of nerves, which accounts for the promotion of cancer stem cell proliferation and the aberrant innervation [92]. Although clinical relevance has been shown for perineural innervation in gastric cancer [92, 93], the detailed molecular mechanisms are not fully understood.

As the luminal surface of intestine is continuously exposed to a variety of potentially damaging factors including toxins and infection, the neurons could interact with intestinal epithelial stem cells to help safeguard, repair and recover from the injury. In the intestine, both enteric neurons and EGCs surround the base of crypts throughout the villi. They also directly contact enteroendocrine cells residing in the epithelium [94, 95]. There is evidence that the ENS stimulates intestinal epithelial growth and repair. Treatment with glucagon-like peptide 2 (GLP-2), a product of intestinal enteroendocrine L-cells, acts on enteric neurons rather than epithelium, which, in turn, stimulates the stem cells in crypts leading to increased proliferation of epithelial cells [96]. Co-culture of intestinal stem cells with enteric neurons and EGCs *in vitro* promotes the differentiation of the stem cells into chemosensory enteroendocrine cells, indicating that the ENS contributes to intestinal stem cell fate determination [97]. EGCs are also thought to play an important role in maintaining the intestinal epithelium barrier. Conditional ablation of EGCs increases mucosal damage and significantly delays mucosal wound healing, whereas EGCs enhance epithelial recovery and cell spreading through soluble proEGF *in vitro* [98]. Molecular mechanisms have been revealed that EGCs secrete 15d-PGJ2, a prostaglandin ligand, and TGF-β1 to inhibit intestinal cell proliferation, while 15d-PGJ2 also promotes intestinal differentiation [99, 100]. Moreover, EGCs release prostaglandin E2 (PGE2) upon activation by tumor cell-derived IL-1 in colon cancer, promoting cancer stem cell-driven tumorigenesis [101]. Thus, not only neurons but also glial cells are functioning in the ENS, which suggests that Schwann cells and satellite cells in the peripheral nervous system may also play a role in the perineural niche of epithelial stem cells.

Perspectives

Investigations of perineural niche in the epithelium tissues described above suggest an important crosstalk via retrograde paracrine signals between epithelial stem cells and neurons. The importance of the crosstalk is not limited in the tissues we addressed above (**Table 1**). For instance, corneal nerves that mostly originate from terminal ganglia (TG) are important for maintaining ocular surface homeostasis and tissue clarity [102-104]. Many diseases affecting cornea can compromise corneal innervation, leading to decreased tear production and blink reflex as well as impaired epithelial wound healing [105-107], thus corneal epithelium is a valuable system to study the perineural niche as well. Skin being the largest sensory organ is innervated by various types of fibers of primary sensory neurons, comprising of mechanoreceptors, nociceptors, and proprioceptors [108]. There are much more to explore for how distinct neurons talk with skin epithelial cells, and participate in the homeostasis and wound healing of skin. Reciprocally, skin derived cues have been found to influence innervation as well [109, 110], making skin an elegant model to study the underlying molecular mechanism that how epithelial cells talk with neurons. More findings are likely to emerge from the characterization of perineural stem cell niche during development and pathogenesis. The application of cutting-edge molecular tracing and single-cell technology may eluci-

Table 1. Crosstalk between nerves and epithelium

Stem Cells	Innervated Neuron Type	Mechanism	Reference
Gli1$^+$ upper bulge hair follicle stem cells	Sensory nerves	♦ SHH derived from sensory nerves supports the upper bulge Gli1$^+$ HFSCs in hair follicle growth during hair cycle. ♦ SHH derived from sensory nerves supports the upper bulge Gli1$^+$ HFSCs in differentiation into epidermal keratinocytes during skin wound healing. ♦ Gli1$^+$ stem cells from adult telogen mice highly express genes that participate in neuron development, differentiation, and synapse maturation.	[33]
Bulge and hair germ stem cell in hair follicle	Sympathetic nerves	♦ External light signals activate bulge and hair germ stem cells by M1-type intrinsically photosensitive retinal ganglion cells-suprachiasmatic nucleus-sympathetic neural pathway. ♦ NE released from sympathetic nerves regulates SHH signaling to activate HFSCs leading to hair follicle regeneration. ♦ Under cold conditions, elevated sympathetic system releases NE triggering the activation of HFSCs in the bulge and hair germ to enter anagen.	[13, 36]
Hair follicle stem cell	Sympathetic nerves	♦ SHH derived from HFSC progeny regulates arrector pili muscle formation and consequently maintains innervation.	[13]
Melanocyte stem cell (MeSC)	Sympathetic nerves	♦ Acute-stress activates sympathetic nerves leading to burst release of NE, which causes quiescent MeSCs to proliferate rapidly. ♦ The proliferated MeSCs is followed by their differentiation, migration and permanent depletion from the niche, resulting in hair graying.	[39]
Gli1$^+$ touch dome stem cells	Sensory nerves projected from dorsal root ganglions	♦ SHH released from sensory nerves maintains and supports the TD and MCs after birth. ♦ Overactivation of SHH signaling in Gli1$^+$ touch dome stem cells induce expansion of K17$^+$ touch dome cells but not MCs.	[46, 47, 50]
K17$^+$ touch dome stem cells	NFH$^+$/TrkC$^+$ nerves projected from dorsal root ganglions	♦ The number of TD afferents is decreased after ablation of K17$^+$ touch dome stem cells rather than MCs.	[42, 53]
Gli1$^+$ Taste bud stem cells	Chorda tympani nerves projected from geniculate ganglion	♦ Ablation of neuronal derived SHH causes a loss of TRCs. ♦ BDNF secreted by TRCs supports taste bud innervation.	[82, 111]
Lgr5$^+$ Epithelial stem cells in the stomach	ChAT$^+$ nerves	♦ Vagotomy suppresses gastric tumorigenesis. ♦ Ach released from epithelial Dclk1$^+$ tuft cells in the early stage of gastric tumorigenesis stimulates Lgr5$^+$ stem cell division via M3R, activates YAP signaling pathway and consequent Lgr5$^+$ stem cell expansion. ♦ Ach induces the secretion of NGF from epithelial cells, which in turn facilitates the growth of nerves producing more Ach. This feed-forward Ach-NGF circuit activates gastric tumorigenesis and offers a compelling target for clinical treatment.	[82, 111]
Lgr5$^+$ Intestinal stem cells	Enteric nerves	♦ GLP-2 derived from intestinal enteroendocrine L-cells, acts on enteric neurons, which stimulates the stem cells in crypts leading to increased proliferation of epithelial cells.	[96, 112]
Intestinal stem cells	Enteric glial cells (one of the components in enteric neuron system)	♦ Conditional ablation of EGC induces crypt cell hyperplasia but worsens intestinal mucosal damage and delays mucosal healing. ♦ EGCs-secreted proEGF activates the focal adhesion kinase in intestinal epithelial cells enhancing epithelial recovery and cell spreading. ♦ EGCs-secreted TGF-β1 inhibits intestinal cell proliferation and increases cell surface area. ♦ 15d-PGJ2 secreted by EGCs inhibits proliferation in intestinal cells but promotes differentiation in them through PPARγ activation.	[98]
CD44$^+$/CD133$^+$ Colon cancer stem cells	Enteric glial cells	♦ Tumor cells stimulate EGCs to acquire a pro-tumorigenic phenotype by the release of IL-1. ♦ IL-1 increases PGE2 production and release from EGCs, promoting colon cancer stem cells proliferation via a PGE2/EP4/EGFR-dependent pathway.	[101]

date further information and better clarify underlying mechanisms.

Nevertheless, further study is required to investigate the communications between nervous system and stem cells in other tissues and organs. The periphery nerves wire environmental cues and mental emotion with stem cell fate in organs of the body. The studies of perineural niche help us better understand how the extrinsic stimuli and our mood affect the tissue homeostasis and disease development. Understanding of the stem cell perineural niche would advance the research of stem cell regulation and the clinical application of stem cells in tissue regeneration. Moreover, these researches will be helpful to understand the effect of mental health like stress on body tissues, as well as the effect of stimuli from outside to the nervous system.

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Disclosure of conflict of interest

None.

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