13 Microbes
New Actors in the Stem Cell Niche

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13.1 INTRODUCTION

The human body hosts, both internally and externally, a huge array of microorganisms that play an essential role in preserving human health. These commensal microorganisms form ecological communities, which are referred to as *microbiota*. The composition of the microbiota depends on the space they occupy and other external/internal factors.

A given host and its microbiota communicate bidirectionally via secondary metabolites, soluble factors, cytokines, and other immune system elicitors to promote tissue homeostasis. A microbiota helps tissues eliminate potentially dangerous pathogens by helping maintain cell function. Pathogen elimination is also aided by cell death and loss, which are necessary to avoid negative consequences to tissue function. Pathogen elimination injures tissues, leading to the activation of tissue-resident multipotent stem cells that replenish lost cells via proliferation and differentiation.

Tissue-resident multipotent stem cells are essential tissue constituents. They help make up the various epithelia that cover the human body, which is continuously exposed to deleterious microbes. The skin and intestinal epithelium are tightly controlled both (i) by intrinsic genetic programs (temporal expression patterns of particular subsets of genes) and (ii) by niche-derived factors originating mainly

from the cell's microenvironment. The *niche* is a specific microenvironment with a specific anatomical location that houses stem cells in an undifferentiated and self-renewable state. Tissue-resident stem cells are multipotent and thereby capable of differentiating into various functional cell types within the tissue. However, they also maintain a constant pool of cells via self-renewal. These stem cells continuously communicate with components of their niche such as terminally differentiated cell types and microbes. They emit and receive instructive signals, which help them preserve their ability to participate in tissue generation, maintenance, and repair.

In this chapter, we illustrate the principles behind the interplay between stem cells and their niche as well as the contribution stem cells that make to tissue development, tissue turnover, and immune response. We discuss two ways in which microbes in the niche influence stem cell activity. They exert direct effects as well as indirect effects when different cells within the stem cell niche are regulated by microbes. After describing the anatomical structure and cellular components of tissues, we present the mechanisms of tissue homeostasis dysfunction or dysbiosis that result from cell function defects and/or a diminished niche structure. We describe how microbes influence the intestinal, respiratory, and dermal epithelia, which are continuously and directly exposed to microbes. We also discuss the influence of gut microbes on distinct stem cells in the nervous system.

13.2 INTESTINE

13.2.1 Drosophila melanogaster

Stem cell proliferation and differentiation occur as a result of harmful host-microbe interactions. The basic principles behind these tissue maintenance mechanisms have been described in the fruit fly *Drosophila melanogaster.* A relatively low complexity of persistent microbiota, a low redundancy of genes, powerful genetic approaches, and the discovery of tissue-resident adult stem cells in the *Drosophila* gastrointestinal (GI) tract have put this model organism to the forefront of research with the aim of understanding the mechanism of host-microbe interactions. These findings are readily transferred to mammalian systems and provide information on the complex pathomechanisms of diseases affecting the GI tract (e.g., inflammatory bowel disease, cancer), which lead to a shortened healthy life span and a serious burden to the patient, the patient's immediate family members, and society.

The GI tract is continually exposed to a variety of microbes and is consequently a primary biological defensive barrier. The intestinal epithelium undergoes constant regenerative episodes in response to stress or damage. Its functionality and a sustained variety of cell types are essential to maintaining barrier function and tissue integrity. Gut tissue maintenance is crucial for preserving both physical barrier integrity and proper immune function, both of which deteriorate in aged flies. Agedness leads to microbial *dysbiosis*, also called dysbacteriosis, when gut microbial flora are imbalanced. Agedness also leads to increased oxidative stress and intestinal stem cell (ISC) dysplasia, which indicates an abnormal development of cells within epithelia (Biteau et al. 2008; Guo et al. 2014). Recent studies revealed that alterations in intestinal microbiota are linked to the development of inflammatory bowel disease

by modulating the host immune function (Manichanh et al. 2012; Sivan et al. 2015). These findings imply that the dialogue between intestinal microbes and ISCs is central to host health.

ISC proliferation must be tightly controlled to avoid the production of damaged, nonfunctional, or supernumerary cells, which are likely to contribute to pathological malformations in the GI tract. Accordingly, intrinsic ISC genetic programs are instructed via many different signaling pathways, which receive inputs from the external environment (niche) and translate these signals into an appropriate cellular response (Figure 13.1). The niche is defined as an anatomic location that produces signals that regulate stem cell behavior. Niches are considered to be dynamically changing (Scadden 2006; Lane et al. 2014).

The continuously renewing GI tract of fruit flies comprises self-renewing ISCs and their daughter cells. These cells are highly similar and functionally redundant to their mammalian counterparts in the stomach, small intestine, and colon. In fruit flies, the epithelial layer is covered by a chitinous peritrophic matrix surrounded by a basal lamina and visceral muscles (Broderick et al. 2014). In the fly gut, ISCs self-renew and, depending on division symmetry, can give rise to either (i) enteroblasts (EBs), which differentiate into mature enterocytes (ECs), or (ii) preenteroendocrine (preEE) cells, which eventually become enteroendocrine (EE) cells (Bonfini et al. 2016) without undergoing further mitotic events. Stem cell division is considered to be symmetric if the daughter cells are identical and asymmetric when the daughter cells differ.

ISCs are multipotent cells with the ability to replenish lost or damaged cells within the entire intestinal epithelium: their daughter cells may differentiate into nutrient-absorbing ECs and hormone-secreting EEs (Ohlstein and Spradling 2007) that contribute to the rebuilding of the tissue during renewal. Proper ISC renewal is controlled by various feedback signaling loops originating from the stem cell niche, which culminates in promoting their proliferation (Figure 13.1). ECs, EEs, and EBs are pivotal players of the ISC niche, which continuously responds to different luminal stimuli (e.g., microbes, chemical insults); hence, their altered activity differentially instructs ISC behavior. For instance, upon *Pseudomonas entomophila* infection or dextran sodium sulfate or bleomycin ingestion, EBs induce Wingless, JAK/STAT (Janus kinase/signal transducers and activators of transcription), cytokine, and EGF (epidermal growth factor) ligand Spitz production, which activate ISC proliferation. Hence, EBs are one of the main sources of growth factors secreted in response to bacterial challenge or chemical stress and so influence ISC proliferation greatly (Cordero et al. 2012). Upon infection with most bacteria, JAK/STAT ligand Upd3 (Unpaired-3) cytokine expression is highly upregulated in ECs via the Hippo, TGF-β (transforming growth factor ß) and SRC-MAPK (mitogen-activated protein kinase) pathways, all of which are required for ISC proliferation (Buchon et al. 2009; Jiang et al. 2009; Houtz et al. 2017).

In recent years, it has become apparent that commensal intestinal bacteria (the microbiota) influence the integrity and physiology of the gut epithelium (Broderick et al. 2014). The complexity of the fruit fly gut microbiome—both of laboratory-raised and wild-caught flies—is lower than it is in mammals and predominantly comprises five to ten bacterial species. The five most frequent bacterial

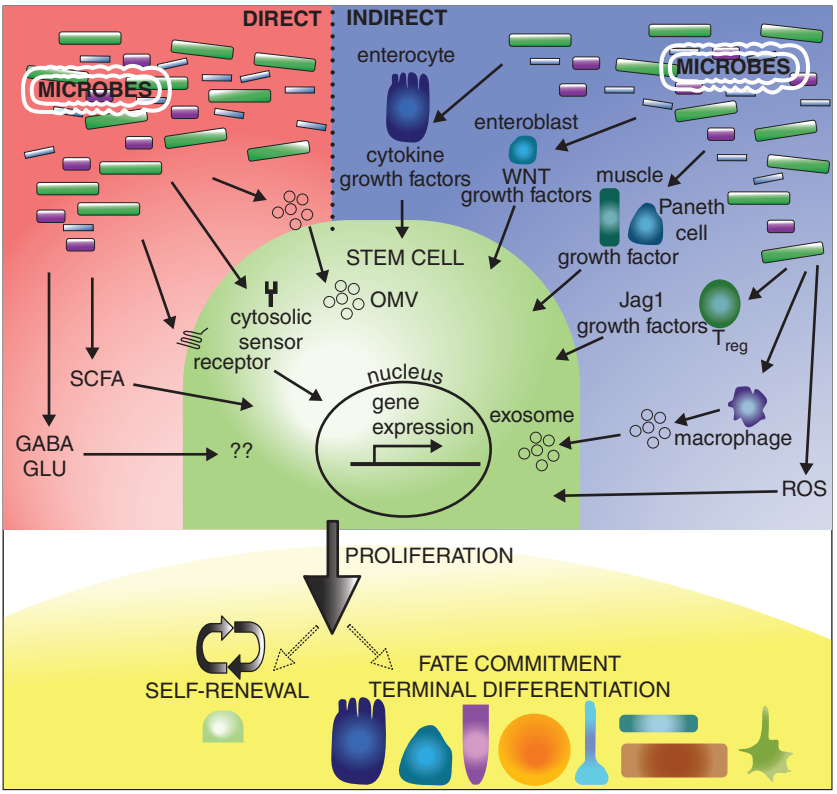

FIGURE 13.1 Microbe-derived niche factors determine stem cell activity. Microbes influence stem cell activity via direct and indirect mechanisms, each of which involves numerous signal pathways: bacterial-produced metabolites (GABA, Glu, SCFA), bacterial cell wall components (peptidoglycans), or outer membrane vesicles (OMVs). Stem cells are usually instructed by the cell types localized in their niche. These cells produce growth/differentiation factors or cytokines/exosomes as part of an inflammatory response triggered by microbes. Stem cells receive and process these niche-derived factors through receptor, cytosolic or organelle sensor-activated signaling, which lead them to change their gene expression. An altered genetic program induces their proliferative response, resulting in a heterogeneous cell progeny, including self-renewed stem cells and fate-committed intermediary cell types, which undergo terminal differentiation to produce the specific functional cell types of a given tissue. See text for further details of the pathways displayed. Abbreviations: GABA, gamma-aminobutyric acid; GLU; glutamate; OMV, outer membrane vesicle; ROS, reactive oxygen species; SCFA, short chain fatty acid; T_{reg}, regulatory T cell.

species are *Acetobacter pomorum, Acetobacter tropicalis, Lactobacillus brevis, Lactobacillus fructivorans*, and *Lactobacillus plantarum* (Broderick and Lemaitre 2012). This microbial community is acquired upon food ingestion and transmitted via defecation or regurgitation (Gilbert 1980).

It is difficult to understand the role of microbes even in conventionally reared (CR) *Drosophila* without manipulating the microbiota. This has prompted a need

to develop and study germ-free (GF) and gnotobiotic flies (i.e., GF flies that are reassociated with known bacterial species by feeding them). Such studies led to the discovery that *A. pomorum* and *L. plantarum* trigger signaling pathways that regulate metabolism and cellular growth (the insulin and target of rapamycin pathways, respectively; Shin et al. 2011; Storelli et al. 2011). Interestingly, a complete lack of intestinal microbes does not impact fly survival, and these flies can be maintained in sterile conditions for generations (Bakula 1969). Aged conventionally reared flies show increased gut microbial diversity as well as higher bacterial titers and increased epithelial permeability (Broderick et al. 2014; Clark et al. 2015). Thus, emerging immunosenescence, or aging-associated deterioration of the immune system, contributes to microbial dysbiosis, resulting in an increased rate of ISC proliferation and improper differentiation, leading to tissue dysfunction (Buchon et al. 2009; Guo et al. 2014).

Transcriptomic studies of GF and CR fly guts revealed that microbiota affects intestinal immune responses and regulates epithelium physiology by activating the immune deficiency (Imd) pathway through NF-κB (nuclear factor kappa-light-chain enhancer of activated B cells) transcription factor–mediated gene expression. This leads to the induction of antimicrobial peptide expression, which limits bacterial growth (Morris et al. 2016). Bacterial cell wall–derived peptidoglycans (a polymer consisting of sugars and amino acids forming the bacterial cell wall) are recognized by peptidoglycan recognition receptors, which are dedicated receptors localized on the surface of ECs. This in turn stimulates Imd/NF-κB signaling, leading to antimicrobial peptide expression and immune tolerance to microbiota (Bosco-Drayon et al. 2012). *Lactobacilli* trigger the production of reactive oxygen species by Duox (Dual oxidase) and Nox (NADPH oxidase) oxidases, providing direct antimicrobial agents and a synergistic component for NF-κB-dependent antimicrobial peptide expression (Ryu et al. 2006; Ha et al. 2009; Lee et al. 2013).

Pathogen-activated Imd pathway in ECs also controls cell turnover in the intestinal epithelium by modulating cell shedding (Zhai et al. 2018). In addition, commensal microbes alter tissue homeostasis (i.e., ISC activity) and modulate metabolism by changing the expression of various digestive enzymes (Broderick et al. 2014; Erkosar et al. 2014) and affecting nutrition in the host (Dobson et al. 2015). Gnotobiotic larvae reassociated with *L. plantarum* or *A. pomorum* show increased protein digestion, as well as elevated amino acid levels in the body and induced growth via insulin signaling (Storelli et al. 2011). Gut microbes also provide dietary vitamin B as a supplement to promote protein nutrition and modulate nutrient acquisition (Chaston et al. 2014; Dobson et al. 2015).

13.2.2 Mice

Murine models also revealed that intestinal microbiota and their products influence ISC activity and affect host nutrition, metabolism, and intestinal epithelial barrier integrity. The structure of the GI tract and the lining epithelia is more complex than in insect guts and includes more compartmentalized regions: the esophagus, gastric region, small intestine, and colon. Most studies focus on the cellular and structural architecture of the small intestine. The intestinal epithelium folds into

tubular invaginations called as Lieberkühn crypts (invaginations into the lamina propria) and into protrusions called villi (projections into the lumen), maximizing the intestinal surface dedicated to digestion and absorption. The murine intestinal epithelium has the tissue with the highest turnover rate in the body and is continuously regenerated every 2–3 days (the human intestinal epithelium is regenerated every 3–5 days) (Clevers 2013). This rapid intestinal epithelial turnover is maintained by the continuous proliferation and differentiation of crypt-based ISCs to replenish lost and damaged cells in the epithelia. This is essential to preserve tissue homeostasis, particularly in response to injury caused by pathogens or chemicals and inflammation when cytokine production is elevated. The niche helps maintain ISC function in response to several microenvironmental factors, including the microbiota, which is considered to be an essential constituent of the ecological niche of ISCs across the length of the intestine (Pedron et al. 2012; Biswas et al. 2015).

Mammalian ISCs self-renew and produce intermediate transit amplifying cells that undergo additional proliferation and differentiation, giving rise to ECs or different types of secretory cells (EEs, goblet cells, and tuft cells) as well as Paneth cells, which localize at the basal side of the Lieberkühn crypt together with ISCs (Li and Jasper 2016). Paneth cells are closely associated with stem cells and secrete antimicrobial peptides, lysozyme, and several niche factors essential for stem cells (Barker 2014). ECs absorb and transport nutrients and secrete enzymes required for the digestion of luminal content. Goblet cells are sources of protective mucus. EEs produce hormones and peptides in response to stimuli (Li and Jasper 2016).

Pioneering studies comparing GF rodents with CR animals revealed changes in the architecture of the jejunum and ileum (anatomically divided subregions of the small intestine). Villus height and crypt depth were decreased, and the mucosal surface and ISC proliferative index were reduced in GF rodents, suggesting a supportive function of microbiota on intestinal epithelia homeostasis (Gordon and Bruckner-Kardoss 1961; Khoury et al. 1969). The recolonization of GF animals with commensal microbes from healthy rodents increased proliferation in the crypt and induced morphological changes reminiscent of the guts of CR animals (Alam et al. 1994). The mice gut microbiome comprises three main bacterial phyla (namely, Firmicutes, Bacteroidetes, and Proteobacteria) according to the 16S rRNA profiling of ileocecal mucosal-associated and luminal bacteria (Rosshart et al. 2017). The importance of the microbial composition was demonstrated by the different effects of *Lactobacillus reuteri* DSM 17938 and *L. reuteri* PTA 6475 on intestinal cell proliferation (Preidis et al. 2012). Several studies carried out in gnotobiotic mice, which are a reassociation of GF mice with single or human-derived bacteria or different bacterial communities, clarified the mechanisms underlying host-microbe interactions (Clavel et al. 2016). These studies highlighted the pivotal roles of commensal intestinal microbiota in maintaining the intestinal structure, leading to a series of exciting discoveries into how microbes affect gut function and epithelial cell activity to support the health of the entire organism.

Intestinal microbes are key niche actors that directly influence gut cells. They also indirectly influence gut cell activity by stimulating cell surface receptors, secreting instructive signals, and producing secondary metabolites or neurostimulatory peptides (Peck et al. 2017). The microbial stimulation of cells in the niche of ISCs

may lead to the production of stem cell regulatory signals, which in turn regulates ISC activity. Toll-like receptor (TLR) activation in Paneth cells by microbes results in the secretion of essential niche-modulating and growth-promoting signals into the crypt (lysozyme, defensins, Wnt, EGF, and Notch) (Bevins and Salzman 2011). *Lactobacillus rhamnosus*, an oral probiotic, improves crypt cell survival after radiation injury via Myd88 (adaptor protein at the intracellular domain site of TLR) and TLR-2 (Ciorba et al. 2012). In response to injury, secreted factors stimulating Wnt signaling provide stem cell–promoting signals: mesenchymal stem cells activate the Wnt pathway or macrophages secrete Wnt-containing exosomes to support ISC growth, which aids in tissue regeneration (Gong et al. 2016; Saha et al. 2016). Gram-negative bacteria produce outer membrane vesicles (OMVs) of a similar size range to exosomes, which are used for cell-cell communication in the stem cell niche (Vanaja et al. 2016). OMVs are taken up by endocytosis and may contain peptides, virulence factors, and RNA/DNA that could potentially alter the activity of the cells in the intestinal epithelia (Kunsmann et al. 2015; O'Donoghue and Krachler 2016). *Neisseria gonorrhoeae*–derived OMVs containing the bacterial outer membrane porin (PorB) targets host cell mitochondria and activates caspase-dependent apoptotic cell death in bone marrow–derived macrophage culture (Deo et al. 2018). Similar cell targeting mechanisms may exist within the dialogue between microbes and intestinal cells, leading to cell loss and thus activating stem cell proliferation and differentiation through a feedback signaling loop.

Intestinal microbiota helps in metabolization and fermentation of food in the gut lumen, and the resulting by-products can be absorbed or act as ligands for different receptors. Intestinal microbiota helps metabolize and ferment food in the gut lumen. The resulting by-products can be absorbed or act as ligands for different receptors. Short-chain fatty acids (SCFAs, 95% of which are produced by intestinal microbes) are the most studied microbe-derived metabolites affecting intestinal homeostasis (Figure 13.1). Butyrate produced in the colon by the fermentation of dietary carbohydrates suppresses colonic stem cell proliferation via Foxo3 (Forkhead box protein O3)-dependent transcription. ECs in the colon (colonocytes) take up microbe-produced butyrate and break it down by shuttling this SCFA for oxidative phosphorylation, thereby generating energy for the cells. ECs are key cellular constituents of the stem cell niche that protect ISCs in the colon from receiving restrictive signals from the niche, which contributes to balanced ISC proliferation in response to environmental cues (Kaiko et al. 2016). Interestingly, butyrate administration to young piglets increased crypt depth and villus length in the jejunum and ileum and promoted the growth of mouse intestinal enteroids in in vitro–generated cultures of ISC-derived small gut organs (Kotunia et al. 2004; Park et al. 2016). Since butyrate-producing microbes primarily reside in the colon, further research is warranted to study the SCFA effect on stem cells of the small intestine. ECs in the small intestine act, not only as a protecting metabolic barrier, like that in the colon, but may also produce proproliferative signals for stem cells in response to microbial stimuli such as Pyy (peptide YY) and Glp-1 (glucagon-like peptide 1) (Mannon 2002; Larraufie et al. 2017). Interestingly, nutrients in the intestinal lumen such as SCFAs are also sensed by EE cells via GPCR (G protein–coupled receptor)-mediated signaling. In response to activating stimuli, EEs produce small peptide hormones that are

released into the intestinal microenvironment and into systemic circulation, which coordinately modulates metabolism and the coordination of local cellular responses in the epithelia (Wong et al. 2016).

Commensal microbiota also produces several neurostimulatory peptides (e.g., neuroactive amines and amino acids; Figure 13.1) that regulate the enteric nervous system, which reciprocally influences the connection between the GI tract and the central nervous system (CNS) (Cryan and Dinan 2012). *L. plantarum, Lactobacillus lactis*, and *Lactobacillus paracasei* produce glutamate (Sano 2009); *Lactobacillus bulgaricus* and *Streptococcus* produce serotonin (Mazzoli and Pessione 2016), and *Lactobacillus, Lactococcus*, and *Bifidobacterium* strains produce GABA (gamma-aminobutyric acid) (Siragusa et al. 2007), which all directly alter the secretory function of intestinal epithelial cells and stimulate the vagal nerve circuit, which in turn may indirectly affect stem cells in the GI tract or in the CNS. Moreover, it is plausible that the gut luminal microbe-derived GABA and glutamate directly act in the CNS by crossing the blood-brain barrier (BBB), although BBB permeability may be affected by stress, diet, and intestinal microbiota (Braniste et al. 2014; Kelly et al. 2015).

In addition to its role in the maturation of the innate and adaptive immune system (Garrett et al. 2010; Tremaroli and Backhed 2012), intestinal microbiota beneficially affects gut epithelial homeostasis, as directly sensed by host receptors such as Toll-like and NOD (nucleotide-binding oligomerization domain–containing protein) receptors (Rakoff-Nahoum et al. 2004; Kufer and Sansonetti 2011). The immune receptor Toll-like receptor 4 (TLR4) is expressed on ISCs where it regulates their proliferation and apoptotic death (Neal et al. 2012). The microbiota directly regulates stem cell activity via the cytosolic innate immune sensor NOD2, which is constitutively expressed at a high level in ISCs and also is involved in gut tissue regeneration after chemically induced tissue injury (Nigro et al. 2014). Intestinal dysbiosis and the deregulated expression of immune receptors are associated with colorectal cancer development (Marchesi et al. 2011; Castellarin et al. 2012).

13.3 LUNG

The mammalian lung is a multicompartmentalized tissue comprising the lower airway of the respiratory system. The lower airway can be divided into two zones: (i) the conductive zone made up of bronchioles and (ii) the respiratory zone containing the alveoli. The airways are topographically exterior to our body, and their surface is constantly exposed to inhaled particles, microbes, and toxins. The wide range of immunogens necessitates sophisticated mechanisms for the elimination of these immune elicitors. The lung epithelium is constructed of various epithelial cells (bronchiolar, lung endothelial, and alveolar), stromal cells, and multipotent stem cells. As a physical defense mechanism, ciliated cells of the epithelium propel inhaled particles and microbes upward toward the pharynx, where the surface mucus traps them. Absence of this directional flow in the airways results in accumulation of bacteria in the mucus in patients with cystic fibrosis, which can lead to serious lung infection (Hart and Winstanley 2002).

Two large discoveries have paved new routes toward understanding how mammalian lung tissue is maintained. First, microbes were identified in the lower airways,

showing constitutional differences upon health status changes (Bernasconi et al. 2016). Second, the lung was found to be a slowly renewing tissue able to undergo regenerative repair in response to wounding (Snyder et al. 2009; Morrisey 2018; Yang et al. 2018). Microbes belonging to two main phyla—Bacteroidetes and Firmicutes—have thus far been identified in the healthy lung (O'Dwyer et al. 2016). Accordingly, the pulmonary epithelium expresses cell surface pattern recognition receptors (PRRs), such as TLRs, which recognize pathogen-associated molecular patterns (PAMPs) presented by viruses, bacteria, and fungi (Lambrecht and Hammad 2012).

Secretory cells within the pulmonary epithelium produce many protective agents. The first set includes defensive antimicrobial mediators (such as lysozyme, defensins, and collectins) (Iwasaki et al. 2017), which eliminate inhaled microbes. The second set includes a wide spectra of specific cytokines (interleukins), which instruct various local cell populations as niche-derived signals to adequately respond (e.g., undergo apoptosis, remodel cell-cell junctions, or proliferate) and to orchestrate the immune response (Lloyd and Marsland 2017). Studying rodent models and human lung development revealed distinct stem cell–like populations along the pulmonary epithelia: basal secretory or club cells (formerly known as Clara cells) in the bronchioles and AEC2 (alveolar epithelial type 2) cells in the alveoli. These cells can self-renew and give rise to daughter cells, thereby replenishing lost or damaged cells after exiting quiescence and subsequently reentering the cell cycle (Snyder et al. 2009; Kotton and Morrisey 2014). In response to injury triggered by infection, the basal stem cells mediate tissue repair via an EGF receptor–augmented mechanism, leading to increased RNase7, antimicrobial peptide, and EGF ligand expression (Shaykhiev 2015). Mechanisms identified thus far that regulate airway stem cell maintenance also include canonical Wnt signaling, PTEN (phosphatase and tensin homolog), GATA-6 transcription factor, and Bmi1 signaling, as well as signaling through the MAP kinase and Ras pathways (Snyder et al. 2009). Though the low mass of airway microbiota makes their characterization difficult, it has become obvious that microbes contribute to health and disease in the airways by providing tonic signals to the cells that respond to such stimuli.

13.4 SKIN

The skin epidermis provides an impermeable protective barrier that defends the body from physical, chemical, and biological insults. Our largest organ, the skin, regulates body temperature and fluid balance and is a complex ecosystem composed of microbial and physical components that occupy different topographical regions. The skin epidermis also plays an essential role in instructing the immune system. Indeed, site-specific colonization is a key feature of the human skin microbiome. According to 16S rRNA sequences, the human skin is predominantly colonized by *Propionibacterium*, *Staphylococcus* spp., *Acinetobacter* spp., *Corynebacterium*, *Proteobacteria*, and *Flavobacteriales* (Grice et al. 2009; Lange-Asschenfeldt et al. 2011).

On the surface of the epidermis, cornified cells (keratinocytes in the upper layer of the epidermis) are continuously sloughed off and replenished after epidermal

differentiation of daughter cell progeny that are produced by stem cells and transient amplifying cells (Fuchs 2008). Keratinocytes guard against microbes via PRRs, TLRs, as well as mannose- and NOD-like receptors. These receptors recognize flagellin, nucleic acid, and lipopolysaccharide from Gram-negative bacteria, peptidoglycan and lipoteichoic acid from Gram-positive bacteria, as well as various fungal cell wall components. The detection of PAMPs activates AMP and cytokine expression in the keratinocytes, leading to bacterial elimination and proliferation in the basal layer (these basal cells are considered to have the ability to self-renew and to give rise to transient amplifying cells) (Grice and Segre 2011). Microbes may also contribute to the host immune response through chemokine production, which instructs epidermal cells in a niche-derived signal on how to orchestrate their response. The commensal bacterium *Staphylococcus epidermidis* eliminates *Staphylococcus aureus* and Group A *Streptococcus* by enhancing host AMP expression, hence contributing to pathogen elimination by cooperating with the host. *S. epidermidis* produces lipoteichoic acid, which induces TLR-mediated responses that inhibit skin inflammation and enable cell survival and tissue repair during infection as well as skin wound closure (Lai et al. 2009, 2010; Linehan et al. 2018).

The hair follicle, which is a specific microenvironment within the epidermis, bears only 25% of the cutaneous bacterial population (97% of these bacteria belong to Gram-positive *Micrococcaceae*; Lange-Asschenfeldt et al. 2011). The hair follicle also contains another type of skin stem cell, quiescent hair follicle stem cells (HFSCs), which reside in the bulge and do not degenerate during the hair cycle. During hair follicle regeneration, HFSCs exit their niche, proliferate, and differentiate. Interestingly, they can be recruited to wound sites to help the epidermis repair (Blanpain and Fuchs 2006). Professional immune cells called regulatory T cells (Tregs) represent an important player of the HFSC niche and contribute to HFSC activation by promoting proliferation and differentiation (Figure 13.1). Treg-derived Jag1 activates Notch signaling as well as other signals such as Wnts, fibroblast growth factors, TGFb2, and PDGFa (platelet-derived growth factor a) in HFSCs upon exit from quiescence followed by their activation (Ali et al. 2017; Horsley and Naik 2017). Importantly, Treg cell migration and hair follicle development were found to be completely dependent on microbial colonization of neonatal mice skin, emphasizing the role of microbe-derived niche signals during hair follicle morphogenesis (Scharschmidt et al. 2015, 2017; Campbell and Koch 2017).

13.5 DISTINCT STEM CELL POPULATIONS—NEURAL STEM CELLS

Here, we discuss the role of neural stem cells in tissue maintenance. This may seem strange, because neural cells, e.g., adult neural stem cells in the CNS, are localized in an immune-privileged space. However, extensive studies revealed an intricate connection between gut luminal microbes and CNS that is likely to contribute to severe neuropathologic changes.

Although the BBB is a vital and highly efficient interface that prevents the highly vulnerable nervous tissue from infections and other toxic agents, extensive studies revealed communication between the GI tract and the brain in conditions such as

anxiety, depression, cognition, and autism spectrum disorder (Sharon et al. 2016). Interestingly, the bidirectional communication between the gut and the brain to regulate neurophysiological behavior is ultimately shaped by gut microbe activity via immune, endocrine, and neural pathways (Cryan and Dinan 2012). Gut microbes regulate the CNS through bacterial secondary metabolites, metabolic precursors, as well as immune and vagus nerve signaling (Sharon et al. 2016). Accordingly, GF mice display defects in working memory and reduced c-fos transcription factor levels, which regulates the cAMP response element–binding protein required for Imd- and Toll immune pathway–dependent infection tolerance and long-term memory formation via the hippocampus (Mizuno and Giese 2005; Gareau et al. 2011; Troha et al. 2018). The hippocampus is a component of the limbic system that is involved in shaping motivation and emotion and plays an essential role in memory formation and spatial navigation. Interestingly, early deleterious changes during several neurological disorders (e.g., neurodegenerative diseases) occur in the hippocampal region of the brain.

Neural progenitor (NSC) cells with hallmarks of stem cell are present in two regions of the adult mammalian brain: the subventricular zone (SVZ) lining the lateral ventricles and the subgranular zone (SGZ) within the dentate gyrus of the hippocampus (Kempermann and Gage 1999; Bonaguidi et al. 2011; Bond et al. 2015). These stem cells give rise to intermediate progenitor cells or transient amplifying progenitors before limited rounds of proliferation, thereby generating neuroblasts that differentiate into neurons and interneurons (Bond et al. 2015). As opposed to adult stem cells of epithelial origin, the main relevance of NSC progeny function is to replace cells following injury to maintain tissue function (Ma et al. 2009). The formation of new cells from adult neural stem cells in the SVZ and SGZ is finely tuned by environmental cues to ensure the integration of newly born neurons into preexisting neuronal circuits that might serve specific neuronal functions (van Praag et al. 1999; Cameron and McKay 2001). In addition, neurogenesis in the SVZ contributes to olfactory bulb maintenance, while neurogenesis in the SGZ is essential for spatial learning, memory formation, and mood regulation (Santarelli et al. 2003; Imayoshi et al. 2008; Zhang et al. 2008).

Adult neural stem cells reside in different neurogenic niches. Firstly, stem cells in the lateral ventricle are interconnected with blood vessels and ependymal cells contacting the cerebrospinal fluid. These cells play an essential role in the metabolism and detoxification of brain and spinal cord cells by circulating nutrients and removing waste (Mirzadeh et al. 2008). Secondly, SGZ neuroblasts communicate via gap junctions and direct cell-cell interactions with each other and with their niche, which consists of endothelial cells and astrocytes (Kunze et al. 2009). Both niches include astroglia, which are specialized cells consisting of astrocytes along with microglia that are sparsely localized in the brain and spinal cord. Astroglia play a central role in regulating NSC self-renewal, fate specification, migration, differentiation, and synaptic integration (Barkho et al. 2006; Jiao and Chen 2008). Microglia are resident immune cells in the brain that constantly scavenge the CNS for plaques, damage, and infectious agents. Microglia are extremely sensitive to stimuli such as lipopolysaccharide, interferon-γ, and tumor necrosis factor-α, which trigger classical activation, resulting in the production of proinflammatory cytokines

and reactive oxygen species to defend nervous tissues from pathogens (Wang et al. 2015). In response to cell damage due to microglia activation, neural cells upregulate adhesion molecules and secrete trophic factors to recruit astrocytes, thereby aiding tissue repair (Gendelman 2002).

13.6 CONCLUSIONS

In this chapter, we described the emerging impact of indigenous and pathogenic microbes on stem cell niches, where they modulate stem cell activity. It is increasingly accepted that microbes regulate stem cell proliferation via both direct and indirect mechanisms, leading to the production of differentiated functional cell types in the given tissue. The influence of microbiomes on stem cells is an intriguing black box in terms of both stem cell biology and microbiota physiology. This demonstrates that the microbial environment of any given stem cell population needs to be accounted for and suggests that a balanced microbial community aids to maintain tissue function and integrity, thus contributing to sustained homeostasis of the whole organism.

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