The principal role of tissue stem cells is to maintain the homeostasis of cycling tissues, in which the stem cell pool remains constant while differentiating cells are continually produced to replenish the loss of differentiated cells. During homeostasis, self-renewal and differentiation must be perfectly balanced to achieve a constant pool of stem cells; this balance can be flexibly modulated in non-homeostatic situations such as the growth of tissues and organs, regeneration after insult, and repopulation after transplantation into the host (Morrison & Spradling, 2008; Watt & Hogan, 2000).

In mammalian testes, robust stem cell functions ensure the continual production of sperm. In testicular seminiferous tubules, spermatogenic stem cells (SSCs) are highly motile and are interspersed between their differentiating progeny, while undergoing self-renewal and differentiation. In such an “open niche” microenvironment, some SSCs proliferate, while others exit the stem cell compartment through differentiation; therefore, self-renewal and differentiation are perfectly balanced at the population (or tissue) level, a dynamics termed “population asymmetry.” This is in stark contrast to the classical perception of tissue stem cells being cells that are clustered in a specialized “closed niche” region and that invariantly undergo asymmetric divisions. However, despite its importance, how the self-renewal and differentiation of SSCs are balanced in an open niche environment is poorly understood. Recent studies have thrown light on the key mechanism that enables SSCs to follow heterogeneous fates, although they are equally exposed to signaling molecules controlling self-renewal and differentiation. In particular, SSCs show heterogeneous susceptibilities to differentiation-promoting signals such as Wnt and retinoic acid. Heterogeneous susceptibility to the ubiquitously distributed fate-controlling extracellular signal might be a key generic mechanism for the heterogeneous fate of tissue stem cells in open niche microenvironments.

**KEYWORDS**
cell heterogeneity, mouse, seminiferous tubules, spermatogenic stem cells, stem cell niche

It is one of the most important goals of tissue stem cell research to determine what mechanism lies beneath such balanced, and coordinated, self-renewal and differentiation of stem cells. An answer to this has been provided by the paradigm of the (“definitive” or “closed”) stem cell niche, as exemplified typically in the *Drosophila* female and male germ lines and mammalian intestinal crypts (Morrison & Spradling, 2008; Simons & Clevers, 2011b; Spradling, Fuller, Braun, & Yoshida, 2011; Stine & Matunis, 2013; Watt & Hogan, 2000). In this paradigm of the definitive niche, stem cells remain undifferentiated because they exclusively receive self-renewing (or anti-differentiation) signals, although they differentiate outside the niche where the self-renewing signal does not work...
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FIGURE 1 Closed and open niche microenvironments. Schematics for “closed” or “definitive” (a) and “open” or “facultative” (b) microenvironments. (a) In a closed niche, self-renewing cells (magenta) are exclusively located in the anatomically defined niche area where niche factor(s) is concentrated (orange dots). Once cells move (or are pushed) out of this area, they undergo differentiation resulting in a spatial recapitulation of the order of differentiation steps (magenta→green→blue, in this case). Here, cells directionally move away from the niche (arrows). (b) In an open niche, self-renewing cells (magenta) are intermingled with differentiating progeny (green and blue) in area where niche factor(s) shows a ubiquitous distribution (orange). Cells should continually interchange their positions, probably through apparently random migrations as observed in the mouse spermatogenesis. See text for more details.

2 | SPERMATOGENESIS IN TESTICULAR SEMINIFEROUS TUBULES

The mammalian testes, which produce numerous sperm over many years or decades, represent a typical example of tissues whose homeostasis is supported by robust and active stem cells, called spermatogenic stem cells (SSCs; also called spermatogonial stem cells). Spermatogenesis proceeds in the convoluted seminiferous tubules (designated as seminiferous tubules hereafter for simplicity), which are tightly packed within the testicular capsule (tunica albuginea) (Figure 2a). In mice, the tubules are separated into >10 loops, in which both ends open to the rete testes (a common outlet for sperm) via a short (<1 mm) stretch of straight seminiferous tubules; their total length in a single testis is approximately 1.7 m, with a diameter up to 200 μm (Nakata et al., 2015; Russell, Ettlin, Sinha Hikim, & Clegg, 1990).

The gaps between the seminiferous tubules are filled with interstitial cells and all types of blood vessels that never penetrate the seminiferous tubules (Figure 2b). The testicular artery branches into pre-capillary arterioles and post-capillary venules run in parallel with the tubules (intertubular arterioles and venules), and accompany abundant interstitial cells including Leydig cells and macrophages (Hilton & Turner, 1993). Capillaries, which do not accompany interstitial cells, typically run circumferentially. Thus, arterioles, capillaries, and venules are composed of a ladder-shape microvasculature structure (Hilton & Turner, 1993; Murakami, Uno, Ohtsuka, & Taguchi, 1989).

Figure 2c illustrates a cross-section of seminiferous tubules showing a composite epithelium of somatic and germ cell types, called seminiferous epithelium. In the somatic component, Sertoli cells develop an epithelium with a prominent network of tight junctions inside the basement membrane, which separates the tubules into basal and adluminal compartments. Peritubular myoid and lymphatic endothelial cells cover the outer surface of the tubules. In the germ cell component, spermatogonia, the germ cells during the mitotic stage including SSCs, are present in the basal compartment that is the gap between the basement membrane and the Sertoli cell tight junction. When meiosis begins, they (now called spermatocytes) translocate to the adluminal compartment, followed by the completion of meiosis and the formation of haploid spermatids, which eventually mature into sperm and are released into the lumen. The entire process of spermatogenesis takes approximately 1 and 2 months in mice and humans, respectively, and is reflected in the four layers of germ cells at different stages of spermatogenesis.

3 | STEM CELL IDENTITY AND CONTEXT DEPENDENCY

SSCs comprise a small subset of spermatogonia located in the basal compartment of seminiferous tubules. Considering the scope and word limit of this review, only a brief overview will be provided for the cellular identity of SSCs; detailed descriptions can be found elsewhere (Yoshida, 2018).
Mammalian SSC research has a long and distinguished history, which was founded by histo-anatomical studies (Clermont & Leblond, 1953; De Rooij & Russell, 2000). A stem cell theory for rodent spermatogenesis termed the "A_s model" was proposed in 1971 and became the prevailing hypothesis in the field (De Rooij, 1973; Huckins, 1971; Oakberg, 1971). In this model, singly isolated mononucleated spermatogonia (called A_single or A_s cells; Figure 3a) are equal to the stem cells, while interconnected syncytia of two (A_paired or A_p) or more (A_aligned or A_al) spermatogonia, resulting from incomplete cytokinesis during mitotic division, are irreversibly committed to differentiate (De Rooij & Russell, 2000). However, recent gene expression analyses have revealed that, in addition to topographical heterogeneity (i.e., variable numbers of interconnected cells), the population of undifferentiated spermatogonia (that share primitive nuclear morphology and are defined molecularly as Kit-negative spermatogonia (Chiarini-Garcia & Russell, 2001; Schrans-Stassen, Van De Kant, De Rooij, & Van Pelt, 1999) include a high complexity of heterogeneity (Yoshida, 2018). In particular, A_s cells are found to be heterogeneous, while the same gene expression signature is shared by subpopulations of A_s and syncytial cells (A_p and A_al). This warrants revisiting the A_s model.

Moreover, as widely believed for tissue stem cells in general, it was also considered naturally that SSCs must be an unequivocally definable entity of cells (e.g., the A_s cells in the A_s model) that always play
roles in whatever context where "stem cells" function, that is, homeostasis, growth, and regeneration. However, live-imaging and pulse-labeling studies have revealed that undifferentiated spermatogonia can flexibly change their behavior in a context-dependent manner, with different fractions of cells acting as "stem cells" under different contexts (Nakagawa, Nabeshima, & Yoshida, 2007; Yoshida, 2012; Yoshida, Nabeshima, & Nakagawa, 2007). Therefore, SSC system is much more complex than originally believed.

Although the identity and functionality of SSCs are under debate (Yoshida, 2018), to the best of my knowledge, the following scheme has been explicitly established by substantial experimental data (Figure 3b). In homeostasis, the SSC function resides within the SSC system (Yoshida, Nabeshima, & Nakagawa, 2007). Therefore, SSC system is much more complex than originally believed.

Although the identity and functionality of SSCs are under debate (Yoshida, 2018), to the best of my knowledge, the following scheme has been explicitly established by substantial experimental data (Figure 3b). In homeostasis, the SSC function resides within the
In this review article, how the GFRα1\(^+\) subset of undifferentiated spermatogonia are maintained in the seminiferous tubules, and how they are engaged in the maintenance of tissue homeostasis, will be emphasized. GFRα1\(^+\) cells comprise 30–40% of the entire undifferentiated spermatogonia (Nakagawa et al., 2010). Although GFRα1\(^+\) cells, as well as the entire undifferentiated spermatogonia, are found over the basal compartment, they show biased localization to the area adjacent to the interstitium that always coincide with the vasculature of arterioles or venules; capillaries and thicker vessels without the accompanying interstitium do not show apparent correlation with these undifferentiated spermatogonia (Chiarini-Garcia, Hornick, Griswold, & Russell, 2001; Chiarini-Garcia, Raymer, & Russell, 2003; Hara et al., 2014; Yoshida, Sukeno, & Nabeshima, 2007). On differentiation, they migrate from this region to spread over the basal compartment, which has been implicated by careful investigation of testis sections and observed directly by intravital live-imaging studies (Chiarini-Garcia et al., 2003; Hara et al., 2014; Yoshida, Sukeno, et al., 2007). Id4-gfp\(^+\) spermatogonia are reported not to be localized near blood vessels (Chan et al., 2014). However, that study counted thicker vessels without accompanying interstitium, which are likely proximal branches of arterioles and veins that occur infrequently (Figure S3 of Chan et al., 2014). Therefore, localization of Id4-gfp\(^+\) and Id4\(^+\) cells relative to the interstitium and arteriole/venule region remains to be elucidated.

In areas of the basal compartment of seminiferous tubules that contain a higher density of GFRα1\(^+\) cells near the interstitium and arterioles/venules, which has been designated as the vasculature-associated niche (Yoshida, Sukeno et al., 2007), GFRα1\(^+\) cells do not cluster to specific regions, but rather intersperse between their differentiating progeny of Ngn3\(^+\) and Kit\(^+\) spermatogonia (Figure 3c,d) (Hara et al., 2014; Ikami et al., 2015). Further, intravital live-imaging has shown that GFRα1\(^+\) cells continually and actively migrate between Sertoli cells and, probably, the differentiating spermatogonia (Figure 3e) (Hara et al., 2014; Yoshida, Sukeno et al., 2007). Therefore, SSCs are regulated in a microenvironment that is different from the authentic “stem cell niche,” which is a specialized region where stem cells are tethered as shown in Figure 1a. In other tissues, such as mammalian bone marrow and the gut of Drosophila, stem cells are similarly intermingled with differentiating progeny, although an anatomically specialized niche region has not been identified explicitly. Such non-canonical microenvironments are collectively designated as an “open” stem cell niche, in contrast to the classical “closed” niche based on their anatomical features (Figure 1b) (Stine & Matunis, 2013). “Open” and “closed” niches are also described as “facultative” and “definitive” niches, respectively, with emphasis on their functional aspects (Morrison & Spradling, 2008). How stem cells are regulated in the “open” or “facultative” niche microenvironment is an as-yet-to-be-elucidated fundamental question.

The intermediate region between convoluted and straight seminiferous tubules, which are connected to rete testes, show distinctive tissue organization. Here, Sertoli cells develop a prominent valve structure that controls the flow of intratubular fluid, which is called the “Sertoli valve.” In this region, Sertoli cells harbor spermatagonia but not more advanced germ cell types. In particular, GFRα1\(^+\) cells are found more densely and may contribute to the spermatogenesis in the neighboring portion of convoluted tubules. Therefore, a property of a “closed niche” is implicated in this interesting region (Aiyama et al., 2015).
5 | POPULATION-ASYMMETRY DYNAMICS OF SSCS IN HOMEOSTASIS

To understand the niche regulation of SSCs, it is essential to know how SSCs select their fate behavior during homeostasis. By nature, this has been achieved only in physiological undisturbed conditions using pulse-labeling and intravital live-imaging studies, based on the tamoxifen-inducible Cre-loxP system and fluorescent proteins, respectively (Yoshida, 2012). When the fate of a single pulse-labeled GFRα1+ cell (or a single syncytial unit of Apr or Aal) was analyzed over time, it did not show a stereotypic pattern but followed a highly variable outcomes: Some GFRα1+ cells produced multiple GFRα1+ cells, while many others exited from the GFRα1+ compartment and produced differentiated (or GFRα1−) progeny only (Hara et al., 2014). Consistent results were obtained from other studies based on different genes, including Ngn3 (Nakagawa et al., 2007), Nanos2 (Sada et al., 2009), and Bmi1 (Komai et al., 2014). However, when fates of many (e.g., >100) clones were collected, their self-renewal and differentiation were perfectly balanced so that the GFRα1+ undifferentiated pool remained constant while constantly producing differentiating cells (Hara et al., 2014; Klein, Nakagawa, Ichikawa, Yoshida, & Simons, 2010). Further, combined with intravital live-imaging and bio-mathematical studies, these quantitative clonal fate data have shown that GFRα1+ cells stochastically (in other words, probabilistically) interchange between mononucleated (A1) and syncytial (Apl or Aal) states via incomplete division and intercellular bridge breakdown (Hara et al., 2014). The intravital live imaging study also revealed that GFRα1+ spermatogonia undergo cell death only rarely (once per approximately 6 months) in homeostasis (Hara et al., 2014). Therefore, the key principle of SSC behavior here is that their multiplication and differentiation are coordinated locally so that their density is stabilized. This type of dynamics is termed as “population asymmetry” (Klein & Simons, 2011).

The dynamics of population asymmetry, which provides good contrast to the authentic “division asymmetry” in which stem cells invariantly undergo asymmetric division that produces self-renewing and differentiating daughter cell pairs, has been revealed to underlie many stem cell-supported tissues as a universal pattern, including mammalian intestinal crypt and interfollicular epithelium regardless of the tissue architecture (Clayton et al., 2007; Doupe, Klein, Simons, & Jones, 2010; Klein & Simons, 2011; Simons & Clevers, 2011; Snippert et al., 2010).

6 | ELEMENTS INVOLVED IN THE OPEN NICHE REGULATION OF SSCS

In the basal compartment of seminiferous tubules, Sertoli cells play an important role in the regulation of SSCs. Sertoli cells are the major source of GDNF (glial cell line-derived neurotrophic factor), the ligand for GFRα1 receptor complex that play important roles in the maintenance of SSCs and spermatogenesis (Hofmann et al., 2005; Meng et al., 2000; Naughton, Jain, Strickland, Gupta, & Milbrandt, 2006; Sato et al., 2011). In situations with increased numbers of Sertoli cells, the number of SSCs was also increased based on the post-transplantation colony formation (Oatley et al., 2011), and a deletion of a downstream effector of Notch, RBPjk, in Sertoli cells results in the increase in the level of Gdnf expression and the number of GFRα1+ spermatogonia (Garcia, Farmaha, Kow, & Hofmann, 2014). Together, these results have led to the prevailing concept that Sertoli cells comprise an essential niche component regulating SSCs via the production of GDNF (Garcia, Parekh, Gandhi, Sinha, & Hofmann, 2017; Hofmann, 2008). Whereas, cell type-specific disruption of Gdnf has suggested that GDNF expression in the peritubular myoid cells is essential for the normal progression of spermatogenesis (Chen, Willis, & Eddy, 2016). Therefore, the production and function of GDNF in the regulation of SSCs requires further in-depth analyses. Sertoli cells also express high levels of Wnt6, a ligand of Wnt/beta-catenin signal that supports the differentiation-primed (Ngn3+) state of SSCs (Chassot et al., 2017; Takase & Nusse, 2016; Tokue et al., 2017). Sertoli cells also play an important role in the retinoic acid (RA) signal that promotes irreversible differentiation to Kit+ spermatogonia, as Sertoli cells and different stages of germ cells cooperatively express the enzymes involved in the retinoid metabolism (Endo, Freinkman, De Rooij, & Page, 2017; Sugimoto, Nabeshima, & Yoshida, 2012; Vernet et al., 2006). According to in vitro studies using cultured spermatogonia and in vivo studies using transient transfection and bead implantation, fibroblast growth factor (FGF) is another important regulator of SSCs (Hasegawa & Saga, 2014; Kanatsu-Shinohara et al., 2003; Masaki et al., 2018; Takashima et al., 2015). This notion is also supported by the analyses of causal mutations for a group of human paternal-age effect genetic disorders (e.g., Apert syndrome and achondroplasia), which has led to the concept of selfish selection of SSCs carrying gain-of-function mutations in the FGF receptor or downstream effector genes that occur in fathers’ seminiferous tubules (Goriely, Mcgrath, Hultman, Wilkie, & Malaspina, 2013; Goriely, Mcvean, Rojmyr, Ingemarsson, & Wilkie, 2003). Although Sertoli cells are implicated as the in vivo source of FGF (particularly FGF2), explicit localization of the expression domain of FGF2 and other FGFs has not been achieved to the best of my knowledge. The expression of FGF family members and their roles in homeostasis warrants further in-depth studies.

In addition to Sertoli cells and myoid cells, macrophages that located in the peritubular and interstitial regions are also involved in the regulation of SSCs (Defalco et al., 2015) (Figure 2c). Finally, the roles of interstitial cells (other than macrophages) and arterioles/veins should be important for SSC regulation, too, given the spatial correlation between these vasculatures and SSCs (Chiarini-Garcia et al., 2001, 2003; La et al., 2018; Yoshida, Sukeno et al., 2007). Furthermore, when a stretch of seminiferous tubules whose accompanying vasculature and interstitium are stripped off were transplanted beneath the testicular capsule of the host mice, vasculature and interstitium were newly formed to nourish the graft in a pattern coordinated with the convolution of the transplanted seminiferous tubules, which should be different from the original pattern in the donor testis. In this situation, SSCs were found to be localized in...
accordance with the new vasculature pattern, indicating that the vessels (arteriols/venules) and/or interstitial cells play causal roles in the establishment of the niche microenvironment for SSCs (Yoshida, Sukeno et al., 2007). The mechanisms underlying this functional link remain to be elucidated at the cellular and molecular levels.

7 | SEMINIFEROUS EPITHELIAL CYCLE: A PERIODIC CHANGE OF MICROENVIRONMENT

The process of spermatogenic differentiation, which takes >35 days to complete in mice, proceeds in a spatiotemporally orchestrated manner (Russell et al., 1990; Yoshida, 2016) (Figure 4). Namely, spermatogenesis, which is synchronized over a cylindrical segment of the seminiferous epithelium, progresses in a periodic manner at regular intervals of 8.6 days; this temporal periodicity is designated as the "seminiferous epithelial cycle" (Leblond & Clermont, 1952) (Figure 4a). Further, since the chronological order of the phase of the cycle (called "stage," separated into I to XII in mice (Russell et al., 1990; Oakberg, 1956) is recapitulated along the tubule length, spermatogenesis is implicated to transmit along the tubule length like a wave (Figure 4b); this spatiotemporal organization is called the "spermatogenic wave" (Russell et al., 1990; Yoshida, 2016). These "cycle" and "wave" ensure the continual production of sperm in a constant proportion of the testis, which must be important for the success of reproduction.

In accordance with the seminiferous epithelial cycle, the aforementioned signals affecting SSCs fluctuate temporally in the basal compartment, in the order of GDNF→Wnt6→RA→GDNF (Figure 4c) (Endo et al., 2017; Grasso et al., 2012; Hogarth et al., 2015; Ikami et al., 2015; Sato et al., 2011; Sharma & Braun, 2018; Sugimoto et al., 2012; Tokue et al., 2017; Vernet et al., 2006). The numbers of GFRα1+, Ngn3+, and Kit+ cells also fluctuate during the cycle (Figure 4d). In contrast, during stages when a certain signal is active, the corresponding ligand (or synthesizing enzymes for RA) shows uniform spatial distribution all around the tubule circumference (Figure 4e–g), suggesting that the entire basal compartment is uniformly exposed to these signals.

It should be emphasized here that homeostasis does not require the system to be completely unchanged and still. Rather, short-term fluctuations (8.6-day cycle in this case) may underlay the persistent stability over much longer timescales (up to years and even decades).
which is an interesting problem from the point of view of both systems biology and stem cell biology. Although temporal fluctuations in the tissue microenvironment may be a ubiquitous phenomenon, such high degrees of synchronization and orchestration are rarely observed, to the best of my knowledge, making the mouse seminiferous tubules a valuable model to address this unexplored question.

8 HETEROGENEOUS SUSCEPTIBILITY TO NICHE SIGNALS AMONG SSCS

In tissues with a closed niche, the spatially restricted distribution of self-renewing factors to the niche region can clearly explain why self-renewing and differentiating stem cells are compatible within a tissue (i.e., inside and outside the niche, respectively) (Figure 1a). In contrast, in seminiferous tubules, the entire basal compartment appears to be ubiquitously bathed with the differentiation-promoting signals (e.g., Wnt6 and RA) during the various stages of the seminiferous epithelial cycle; however, importantly a proportion of spermatogonia remain undifferentiated (Figure 4d). The mechanisms underlying such a robust heterogeneous (or asymmetric) fate of SSCs, which determine if the SSCs differentiate or not, needs to be elucidated.

Recent studies have provided important clues to answer this question, as is schematically summarized in Figure 5. During the seminiferous epithelial cycle, as shown in Figure 4c,d, an increase in Wnt6 coincides with the prominent GFRα1 to Ngn3+ transition, consistent with the idea that Wnt6 promotes differentiation via activation of the beta-catenin pathway; however, not all GFRα1+ cells differentiate, and a significant number of these cells remaining undifferentiated (Tokue et al., 2017). Tokue et al. (2017) further questioned why only a proportion of GFRα1+ cells become Ngn3+, while others remain undifferentiated, even though all cells are exposed to Wnt6. They identified Shisa6 as a novel Wnt inhibitor acting in a cell-autonomous manner that shows highly restricted expression in a small part (~1/4) of GFRα1+ cells. Disruption of Shisa6 significantly reduced the SSC compartment when the beta-catenin signal was elevated using degradation-resistant form of beta-catenin (Harada et al., 1999). These findings support the idea that Shisa6 cell-autonomously "protects" a subset of SSCs from differentiation-induction by the Wnt/beta-catenin signal elicited by ubiquitously distributing ligand such as Wnt6 (Figure 5a).

The combination of "ubiquitous signal" and "heterogeneous susceptibility" also play a role in the next step of differentiation. Ikami et al. (2015) found that only Ngn3+ cells, but not GFRα1+, cells differentiate in response to RA, through the lineage-tracing studies of GFRα1+ and Ngn3+ spermatogonia combined with manipulation of RA signal using a vitamin A-deficient mouse model (Van Pelt et al., 1996). In consistent with this, RARγ, a receptor for RA playing a major role in spermatogonia (Gely-Pernot et al., 2012), is specifically expressed in Ngn3+ cells. Ectopic expression of RARγ in GFRα1+ cells, which normally do not express RARγ, caused an RA-induced differentiation to Kit+ cells that skipped the Ngn3+ state. Thus, the presence or absence of RARγ determines the cell fate—whether to differentiate or not, respectively—regardless of ubiquitous exposure to RA.

These studies illustrate the importance of inhomogeneous susceptibility for ubiquitously distributing differentiation-promoting factors as a key mechanism underlying the fate asymmetry of SSCs in testicular open niches during multiple steps of differentiation. Interestingly, the inhomogeneous responses are mediated by different molecular mechanisms, that is, inhibitors and receptors.
The importance of cell heterogeneity in the regulation of SSCs in the testicular open niche microenvironment has been illustrated. Findings regarding the SSC heterogeneity have been accumulated rapidly over the past few years, based on the evolutionary progress of single-cell omics methodology. The combination of this essentially static information and dynamic information obtained by lineage-tracing and/or live-imaging studies should be extremely powerful, which will greatly accelerate our understanding of SSC regulation in the testicular open niche microenvironment.

To conclude, several fundamental questions need to be addressed in future studies. First, the origin of heterogeneity is of particular interest, that is, is it from the "stochastic fluctuation" that is intrinsic to the gene network that includes SSCs? How much does the interplay between the intracellular gene network and extracellular signals contribute to SSC heterogeneity? Second, the underlying mechanisms and biological significance of the preferential distribution of SSCs to interstitium/vasculature is also intriguing. Third, the mechanism responsible for the dynamics of population asymmetry, in which self-renewal and differentiation occur stochastically but are perfectly balanced so that the SSC pool size (i.e., the average density) remains constant, is of particular interest; this is a central question for open niche-supported tissues in the field of tissue stem cell biology in general. Finally, it must be determined what is common and what is special for open and closed niche-supported stem cell systems, which have been considered as being distinctive and contrasting entities but instead could possibly be representing opposite extremes of a continual entity of stem cell-supporting microenvironments.

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