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The stem cell niche: theme and variations

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Stem cells in animal tissues are often located and controlled by special tissue microenvironments known as niches. Studies of stem cell niches in model systems such as *Drosophila* have revealed adhesive interactions, cell cycle modifications and intercellular signals that operate to control stem cell behavior. Candidate niches and regulatory molecules have also been identified in many mammalian tissues, including bone marrow, skin, gut and brain. While niches are an ancient evolutionary device with conserved features across diverse organisms, we suggest that certain niches display important differences in their organization and function.

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Abbreviations

Bam	bag of marbles
BMP	bone morphogenetic protein
Dpp	decapentaplegic
Gbb	glass bottom boat
GEP	gastric epithelial precursor
GSC	germ line stem cell
HSC	hematopoetic stem cell
IGF	insulin-like growth factor
SSC	somatic stem cell
SVZ	subventricular zone
VEGF	vascular endothelial growth factor

Introduction

The notion that tissue stem cells reside within specific anatomical locations termed 'niches' arose nearly four decades ago from studies of transplanted hematopoetic progenitors [1]. The likely existence of microenvironmental factors produced by niche stromal cells has long cautioned that some aspects of stem cell biology may be difficult to deduce from purified stem cells. When the first niche to be defined at the cellular and functional level was described in the *Drosophila* ovary [2], stem-cell-extrinsic factors were indeed found to play a paramount role. Subsequently, stromal microenvironments likely to act as niches have been associated with an increasingly wide and diverse set of stem cells (Table 1). Hematopoetic stem cells (HSCs) reside in niches located in trabecular bone where they contact osteoblasts. Stem cells maintaining the multiple cell types of the mammalian digestive tract map to precise locations within discrete substructures (e.g. gastric units or intestinal crypts). Epidermal stem cells with the potential to replenish basal keratinocytes, hair and sebaceous glands are found in the hair follicle bulge. Ongoing cell production in the adult mammalian brain depends on astrocytes that reside in special niches within the subventricular zone of the cerebellum and the subgranular zone of the hypothalamus. These findings have already expanded the focus of stem cell research and deepened our understanding of how cell production is regulated *in vivo*.

The structure and properties of the best-characterized niches have been reviewed recently [3–5]. Despite this, our knowledge of niches remains limited. Variations in niche anatomy and regulatory mechanisms are just beginning to emerge. Here we consider recent studies of stem cell niches and suggest that multiple subtypes of niche may exist. Discerning such differences is likely to help us better understand how these remarkably small, simple units influence tissue growth, repair and aging.

Simple niches

We define a stem cell niche as 'a specific location in a tissue where stem cells can reside for an indefinite period of time and produce progeny cells while self-renewing'. Many recently characterized niches, especially those in gonadal, epithelial and digestive tissue, appear to be surprisingly simple in structure and to operate using common mechanisms (Figure 1a). Often, specific junctions anchor a small number of stem cells adjacent to particular stromal partner cells (Table 1). In several tested cases, adherens junctions are involved [6••,7], while interactions with extracellular matrices are suspected to play a role [8]. Tight association with a permanent cell probably locks the stem cell in place and positions it to receive one or more critical intercellular signals. Transduction of certain intercellular signals in stem cells, for example bone morphogenetic protein (BMP) reception in *Drosophila* germ-line stem cells (GSCs), directly controls growth and inhibits differentiation (see below). Wnt signaling may play a similarly direct role in regulating stem cells in the mouse intestinal crypt [9••]. Other signals may coordinate stem cell activity with developmental cycles or nutritional variations. Not every signal

Table 1

Stem cell niches.

Niche	Stem cell	Partner cell	Stem cells per niche	Important proteins	Junction	Gene profile	Other references
Drosophila ovariole	GSC	Cap cell	2–3	BMP, Nanos	DE-Cad, β-Cat		[12•,20,41]
Drosophila testis	GSC	Hub cell	7–15	JAK-STAT, BMP	DE-Cad, β-Cat		[37,38•]
Mouse testis	GSC			BMP, Nanos, Plzf		[42,43]	[11,43–45]
Mouse bone marrow	HSC	Osteoblast		BMP, Notch-1, Sca-1, Bmi-1	E-Cad, β-Cat, Rac1, Rac2	[46–48]	[13••,14••,15, 30,33,49]
Mouse intestinal crypt	IEP		1–2	Wnt, Shh		[50]	[9••]
Mouse gastric ismus	GEP			IGF		[22]	[22]
Drosophila ovariole	SSC	Inner sheath cell	1	Hh	DE-Cad, β-Cat		[7,24]
Mouse skin	IESC	Dermal papillae		BMP			[51]
Mouse hair follicle bulge	ESC		>50	c-myc, p63, Wnt, RBP-J	Integrin, β-Cat	[25••,52]	[8,17,25••,53,54]
Mouse hair follicle	MPC			BMP, Wnt, Shh			[51,55,56]
Mouse hair follicle	Melanoblast			SCL/c-kit	E-Cad, β-Cat		[26•,57]
Mouse lateral ventricle	SVZ astrocyte	Ependymal, vascular cells; astrocytes		Shh, Noggin, Bmi-1, TLX	N-Cad, β-Cat	[46,47]	[6••,21••,29,31, 58,59]
Mouse hippocampus	SGZ astrocyte	Vascular cells astrocytes		Shh, VEGF, Bmi-1, TLX, MBD1, NSRE	N-Cad, β-Cat		[6••,18,19,29, 31,59–62]

β-Cat, β-catenin; Cad, cadherin; ESC, epithelial stem cell; Hh, hedgehog; IEP, intestinal epithelial precursor; IESC, interfollicular epithelial stem cell; JAK/STAT, Janus kinase signaling pathway; MBD1, Methyl-CpG binding protein 1; MPC, matrix progenitor cell; SGZ, subgranular zone; Shh, Sonic hedgehog.

whose loss affects stem cell function will necessarily qualify as a stem cell regulator. Intercellular signals are a ubiquitous feature of tissues and in some cases may simply play general roles maintaining tissue physiology and/or cellular differentiation. Finally, niches must ensure that daughter cells differentiate appropriately as they leave the niche. The *Drosophila* testis recently joined those systems known to employ oriented divisions to direct stem cell daughters away from the stem cell microenvironment [10•].

A true stem cell niche constitutes a stable aspect of tissue anatomy whether or not stem cells are present. Indeed, the ability of 'empty' niches to re-acquire and maintain introduced stem cells remains the definitive proof of their existence. Such assays have been carried out in the bone marrow, spleen and testis of the mouse and in the *Drosophila* ovary [1,11,12•]. In the ovary it has been possible to show that ectopic cells return to the exact location of the original stem cells at the cellular level.

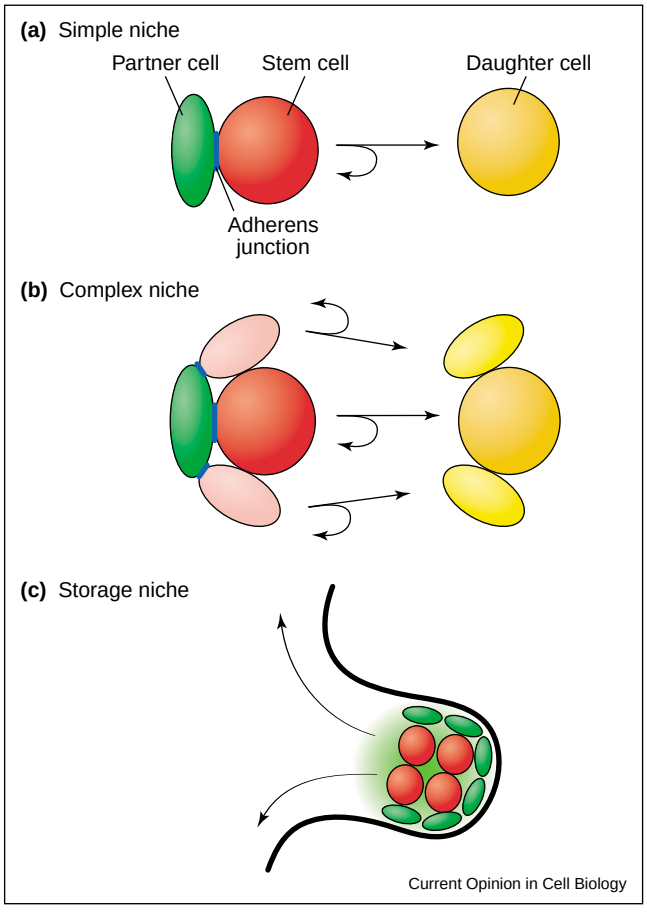
Stem cell loss and replacement within simple, anatomically defined niches is not confined to experimental assays, but appears to be a major mechanism ensuring a stable and long-lasting supply of progenitors. Replacement of lost stem cells in the *Drosophila* ovary by rare symmetric divisions of an adjacent stem cell maintains stem cell number *in vivo* [2]. Similar behavior is likely to occur in mammalian testes, as stem cell niches are filled first within a region of the seminiferous tubule following introduction of germ cells [11]. Such a system not only ensures that lost stem cells will be replaced, but keeps stem cell numbers near maximum by quickly eliminating empty niches. Some tissues appear to regularly construct new niches to maintain an adequate stem cell supply. For example, bone is continually undergoing remodeling, and it is precisely in these areas that HSCs are enriched [13••,14••]. HSC number responds to changes in the number of osteoblasts [14••,15]. New intestinal crypts [16•] and new hair follicles [17] can be generated *de novo*. Any stem-cell-based tissue that is capable of growth is likely to have the capacity to produce new niches.

Complex niches

Some niches appear to be more complex than the relatively simple examples described above. For example, subventricular zone (SVZ) neural stem cells closely associate with and sometimes specifically contact other astrocytes, neuroblasts, ependymal cells, endothelial cells and a factor-rich basal lamina [18–20,21••,4]. The great cellular complexity of the nervous system may require that stem cell activity be subject to more controls than are required for other tissues. Indeed, the complex shape and junctional specializations of neural stem cells may facilitate diverse, wide-ranging interactions. While most other stem cells seem simpler in structure, suspicion is growing that they may be able to communicate with muscle, nerve and connective tissue cells surrounding the niche proper, and via humoral factors. For example, HSCs, gastric epithelial precursors (GEPs), somatic stem cells (SSCs) and probably other stem cells respond to insulin-like growth factors (IGFs) [22–24].

Complexity may also arise when multiple stem cells reside within a niche (Figure 1b). Several different stem

Figure 1



Proposed niche types. **(a)** Simple niche. A stem cell (red) is associated with a permanent partner cell (green) via an adherens junction (blue). The stem cells divides asymmetrically to give rise to another stem cell and a differentiating daughter cell (orange). **(b)** Complex niche. Two (or more) different stem cells (red and pink) are supported by one or more partner cells (green). Their activity is coordinately regulated to generate multiple product cells (orange and yellow) by niche regulatory signals. **(c)** Storage niche. Quiescent stem cells are maintained in a niche until activated by external signals to divide and migrate (arrows).

cells have been localized in the hair follicle bulge, but it is not known if they interact [25••,26•]. Stem cell–stem cell communication is likely in the *Drosophila* testis, where separate stem cells for germ cells and for somatic cyst cells lie in contact [27]. While coordinated activity of these stem cells has yet to be demonstrated at the single cell level, both stem cell types must divide to generate a new spermatogonial cyst containing one germ cell and two cyst cells. It may be that niches should not be thought of as units of stem cell maintenance, but rather as units of production of specific cellular outputs — spermatogonial cysts, ovarian follicles, intestinal villi, etc. If so niches might be expected to contain whatever stem cells and coordination mechanisms are adequate for the job.

Seemingly simple niches may exhibit complex temporal behavior. For example, it may be possible to support new stem cells without maintaining any special, pre-existing stromal architecture ('empty niches'). Local structures to anchor and maintain new stem cells might simply be induced following stem cell arrival. Finally, some tissues may have the capacity to support stem cells without any anatomical specializations beyond a large expanse of basement membrane. The basement membrane of mammalian epidermis or seminiferous tubule may fall in this category. If stem cells can be supported by spatially uniform signals and non-specific stromal contacts alone, it would follow that niches are sometimes unnecessary for stem cell maintenance or else that they can be extraordinarily large.

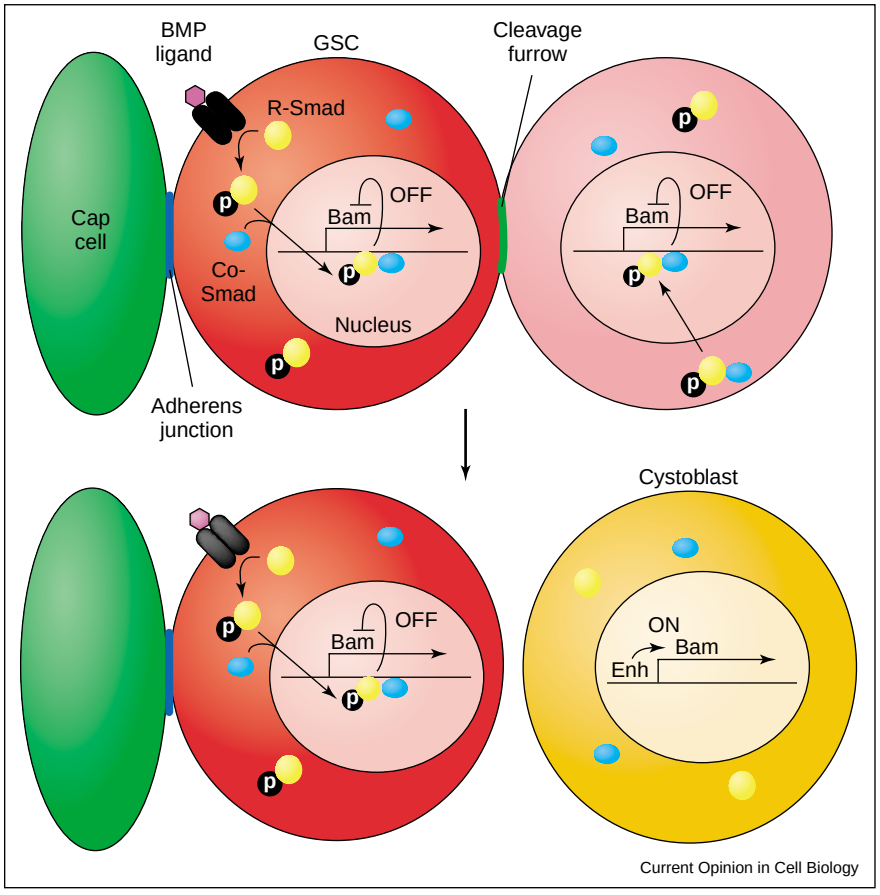
Storage niches

A potentially different type of niche, the 'storage niche', may contain quiescent stem cells (Figure 1c). The bulge region of the mouse hair follicle currently represents the canonical example of such a niche. During most of the hair cycle and in the absence of wounding, transient epithelial stem cells and melanoblasts in the basal keratinocyte layer and the hair follicle matrix support ongoing skin and hair production. Reserve stem cells located in the bulge do not divide during this period and hence can preferentially retain labeled DNA, a trait often associated with stem cells. Following wounding or hair cycle completion, however, sub-populations of bulge stem cells activate, exit the niche, and migrate to the site of damage or stem cell loss [25••]. Melanoblast progenitors are also stored in or just below the bulge [26•]. It is not known whether bulge stem cells comprise distinct subtypes or interact with each other and/or partner cells, or even whether they migrate directly out of the niche or only send their daughters to serve as new transient stem cells. Likewise, the adhesive contacts and molecular signals that mediate their responses have not been characterized. Storage niches may simply be normal niches that are located in favorable, damage-resistant regions or they may contain unique mechanisms to facilitate the safe maintenance of quiescent cells.

Programming daughter cells

Niches with active stem cells must contain routes for progeny cells to exit lest they burgeon into tumorous nodules. For example, HSC daughters move away from the osteoblasts of the trabecular bone and toward the center of the marrow, while spermatogonia leave the basal layer and migrate toward the lumen of the seminiferous tubule. We consider a cell to have left the niche when it reaches a location that cannot itself support a stem cell because one or more critical adhesive or signaling factors is no longer present. Even before it has done so, the daughter cell may begin to differentiate. Thus, niches are likely to contain specific structural features and

Figure 2



Model for regulation of cystoblast differentiation in the *Drosophila* GSC niche. A stem cell (red) associated via an adherens junction with a cap cell (green) is shown that is still attached to its daughter (pink) via an incomplete cytokinesis furrow. BMP signaling (purple hexagon) from the cap cell is received only by the adjacent stem cell. Activated BMP receptors (black) phosphorylate an R-Smad (yellow), which complexes with a Co-Smad (blue) and translocates into the nucleus of both the stem cell and its interconnected daughter (pink). The complex then binds to the silencer element of the *bam* gene and represses its transcription. When the stem cell daughter completes cytokinesis, the supply of phosphorylated R-Smad is cut off and the *bam* gene soon becomes de-repressed, initiating cystoblast differentiation (yellow cell).

mechanisms designed to ensure appropriate daughter cell movement and to initiate differentiation.

Daughter cells continue to divide and specialize long after leaving the niche; hence it is technically very difficult to sort out the relatively rare niche-specific differentiation mechanisms. Gene profiling studies are currently being used to identify candidate genes expressed differentially in stem cells or their progeny (see Table 1). The difficulty of obtaining highly pure cell populations remains the major obstacle to this approach. Although no common molecular processes ('stem cell genes') have yet been identified, some candidate molecules likely to control the differentiation of particular daughter cells are beginning to emerge. For example, Bmi-1 and TLX encode putative transcriptional regulators that may play a key role regulating HSCs and possibly neural stem cells [28–31]. HSCs also require Wnt signals [32] and are modulated by Sca-1 [33].

Our knowledge of the mechanisms by which stem cell daughters are programmed has progressed furthest in studies of the *Drosophila* ovarian cystoblast (Figure 2). The *bag-of-marbles* (*bam*) gene is necessary and sufficient for the cystoblast fate; this gene is normally off in stem cells and young daughters (pre-cystoblasts). Consequently, daughter programming involves the differential activation of *bam* expression only in the stem cell daughter that will become a cystoblast. Stem cells lie adjacent to cap cells, a site that for unknown reasons strongly favors BMP signal reception [12•]. BMP receptor activation in stem cells directly represses *bam* transcription [34••,35]. Consequently, the stem cell daughter that loses cap cell contact will downregulate BMP signaling, upregulate Bam expression and acquire a cystoblast fate.

Prolonged cytokinesis, a cell cycle modification characteristic of all early germ cells [36••], appears to provide a

final, sophisticated level of control (Figure 2). There is a strong temporal correlation between furrow closure, loss of daughter cell BMP signal reception and the onset of daughter cell *bam* expression. This suggests that *bam* transcription can continue to be repressed through the open cytokinesis furrow, possibly by the movement of active Smad complexes. Using furrow closure as the final switch to shut off the BMP signal and to initiate cystoblast differentiation may ensure that daughter cells have fully separated before transcribing a gene (*bam*) that could cause their stem cell mothers to differentiate.

Gonialblasts, the GSC daughters in the *Drosophila* testis analogous to cystoblasts in the ovary, have recently been shown to utilize this pathway as well. Male GSCs, like female GSCs, do not express Bam, and recent studies demonstrate that high Bam levels cause male GSCs to differentiate [37,38•]. Furthermore, BMP signaling is activated in male GSCs by Dpp (decapentaplegic) and Gbb (glass bottom boat) ligands and acts to represses *bam* expression, as in female GSCs [37,38•]. Unlike in the ovary, however, Bam is not immediately required to initiate goniolblast divisions, and evidently other genes contribute to gonialblast specification and development. Once formed, reciprocal signals between gonialblasts and somatic cyst cells promote continued differentiation [39].

Stabilizing daughter cell fates

A stem cell daughter that encounters an empty niche can sometimes enter and become a stem cell again. Most cells, by contrast, once they have begun to differentiate, appear to be precluded from reverting, at least under normal conditions. Recently, Kai and Spradling [36••] showed that interconnected germ cells in four- and eight-cell cysts can detach from their neighbors and revert to fully functional stem cells with very high efficiency when placed in the context of a larval ovary, or an adult germ cell tumor. Brawley and Matunis [40••] induced stem cell differentiation by shifting $STAT^{ts}$ flies to the non-permissive temperature, and then looked for reversion of the remaining cysts following a return to normal temperature. They observed that male cystocytes (spermatogonia), like female cystocytes, could revert into apparently functional GSCs. Interestingly, somatic stem cells were always restored as well, suggesting that they might play some role in the reversion process. These studies clearly show that stem cell daughters do not immediately lose the capacity to function as stem cells. In each stem cell lineage, specific mechanisms are probably required to stabilize the early steps of differentiation, steps that can sometimes be reversed when these mechanisms are absent or are overridden. Transit amplifying cells often greatly outnumber stem cells *in vivo*; thus, these cells are likely to represent a valuable source of replacement stem cells for normal or therapeutic tissue repair.

Summary

Niches have emerged as a major mechanism of stem cell regulation. Our knowledge of niches remains very limited, but is starting to grow and solidify. Discerning differences such as those proposed in this review may help reveal how these remarkably small, simple units influence tissue development, growth, repair and aging.

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