Special Focus: Stem Cells

Anchoring stem cells in the niche by cell adhesion molecules

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Abbreviations: ECM, extracellular matrix; GSC, germline stem cell; FSC, follicle stem cell; ISC, intestinal stem cell; HFSC, hair follicle stem cell; HSC, hematopoietic stem cell; NSC, neural stem cell; SSC, spermatogonial stem cell; MaSC, mammary stem cell

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Adult stem cells generally reside in supporting local microenvironments or niches, and intimate stem cell and niche association is critical for their long-term maintenance and function. Recent studies in model organisms especially Drosophila have started to unveil the underlying mechanisms of stem anchorage in the niche at the molecular and cellular level. Two types of cell adhesion molecules are emerging as essential players: cadherin-mediated cell adhesion for keeping stem cells within stromal niches, whereas integrin-mediated cell adhesion for keeping stem cells within epidermal niches. Further understanding stem cell anchorage and release in coupling with environmental changes should provide further insights into homeostasis control in tissues that harbor stem cells.

Tissue-specific adult stem cells are characterized by their prolonged self-renewal ability and potentiality to differentiate into one or more types of mature cells. These unique properties make stem cells essential for maintaining tissue homeostasis throughout life. It is generally believed that all adult stem cells reside in specific microenvironments named niches, which provide physical support and produce critical signals to maintain stem cell identity and govern their behavior. Consequently, intimate stem cell and niche association is a pre-requisite for stem cell’s long-term maintenance and function. How stem cells are kept within the niche is thus an important issue in stem cell biology. Characterization of a number of stem cell niches in model organisms has led to the classification of niches into two general types: stromal niches where stem cells have direct membrane contact with the niche cells and epidermal niches where stem cells are usually associated with the extracellular matrix (ECM), and do not directly contact any fixed stromal cells. Studies in Drosophila have led to the cellular and functional verification of the stem cell niche theory and surprisingly, have also led to the discovery of the molecular mechanisms anchoring stem cells to the niche. Here I consider recent studies in Drosophila on types of cell adhesions used to anchor stem cells in the niches, and summarize cell adhesion molecules utilized in the most characterized niches in the mammalian tissues, and suggest that cadherin-mediated cell-to-cell adhesion and integrin-mediated cell-to-ECM adhesion are possibly two general mechanisms that function in respective stromal or epidermal niches for stem cell anchorage in diverse organisms.

Cadherin-Mediated Cell Adhesion in Drosophila Germline Stem Cell Niche

Cadherins are a large family of transmembrane glycoproteins, which form calcium-dependent homophilic adhesion on the extracellular domains to mediate cell to cell adhesion. Cadherin-mediated cell adhesion is involved in cell rearrangement in embryos as well as adult tissues during regeneration and maintenance, and is important for tissue integrity. Cadherin expression on the cell membrane is able to mediate weak cell to cell adhesion, but cadherin clustering on the membrane and forming junctional structures produces strong adhesion activity to sustain mechanical stress. In this case, the cytoplasmic domain of cadherin is associated with regulatory proteins, including β-catenin and α-catenin to link actin cytoskeleton, which in turn facilitates the formation of junctional structures.

The first functional evidence for an essential role of cadherin-mediated adhesion in a stem cell niche came from the study of germline stem cells (GSCs) in the Drosophila ovary. The GSC-niche unit is localized at the anterior tip of an ovariole, where 2 to 3 GSCs are anchored to a tight cluster of 5 to 6 non-dividing stromal cells named cap cells (Fig. 1). The cap cells produce essential self-renewal signals to control GSC maintenance and differentiation, and thus constitute the GSC niche (Fig. 1). GSCs are anchored to the niche through DE-cadherin-mediated adhesion between GSCs and cap cells, which is supported by several lines of evidence as follows. DE-cadherin molecules are highly accumulated at the membrane contact between GSCs and cap cells. Functional removal of shotgun (shg, the gene encodes DE-cadherin) or Armadillo (the gene encodes Drosophila β-catenin)
in GSCs causes GSC detachment from their niche and differentiation. Moreover, under transmission electron microscopy, dense foci representing adherens junctions are observed between cap cells and GSCs. Adherens junctions probably also mediate the anchorage of the mitotic spindle for asymmetric stem cell division to ensure that after a cell division, one daughter remains in contact with the niche (to become a new stem cell) and the other leaves the niche and differentiates. In Drosophila male GSCs, adherens junctions at the GSC-hub interface are associated with adenomatous polyposis coli (APC) proteins that mediate spindle anchoring for asymmetric stem cell division. Similar components are also required for proper spindle anchoring in syncytial blastoderm and neuroepithelial cells. It is suggested that Cadherin also participates in GSC competition for niche occupation. GSCs that are homozygous mutant for *bam* or *bgcn* gene, two essential differentiation-promoting genes, are more competitive in occupying the niche. Although cell division rate might play a role in stem cell competition, DE-cadherin is upregulated in *bam* or *bgcn* mutant GSCs, which presumably causes enhanced adhesion to the niche and consequently cell competitiveness for niche occupation.

Notably, some *shg* mutant GSCs can be maintained within the niche when both GSCs are mutant within the same niche, a situation that makes cell competition disadvantage less apparent. This indicates that other cell adhesion molecules, such as cadherin-like or immunoglobulin-like molecules might play partially redundant functions for anchoring GSCs in the niche.

In addition to GSCs, cadherin-mediated cell adhesion is also required for anchoring follicle stem cells (FSCs) in the Drosophila ovary and somatic cyst stem cells in the Drosophila testis. It is imaginable that, although junctional structures safely anchor GSCs, they must be dynamically regulated. GSCs exhibit limited half-life of 4 to 5 weeks. When an old GSC starts to leave the niche, adhesion must be disassembled. Conversely, when the neighboring GSCs divide symmetrically to generate a new stem cell for replacement, adherens junctions must be quickly reassembled. Cadherin function can be regulated and affected by many cellular processes and signaling, such as actin cytoskeleton assembly and endocytosis. Consistently, dysfunction of these processes causes defective cell adhesion and subsequently stem cell loss from their niches.

**Integrin-Mediated Cell Adhesion in Drosophila Follicle Stem Cell Niche**

Integrins are a large family of cell surface receptors that mediate adhesion between cells and ECM by linking the ECM molecules to the actin cytoskeleton. They are transmembrane heterodimers composed of one α subunit and one β subunit, and both are indispensable for their function. The Drosophila genome encodes totally 5α subunits (αPS1-5) and 2β subunits (βPS, βv), comparing to 18 subunits and eight subunits in the mammalian genome that known to assemble at least 24 different integrins. Integrins are essential for many developmental processes, including cell migration and morphogenesis, cell differentiation and organogenesis, and maintaining tissue architecture and integrity. Integrins may also play important roles in stem cells, as specific integrin subunits have enriched expression in many mammalian stem cell populations, and integrin-mediated adhesion to the basement membrane has been implicated in controlling various stem cell behaviors, including cell anchorage, cell survival, migration and differentiation. However, due to functional redundancy and limited characterization of stem cell niche structures, clear functional requirements in mammalian stem cell niches are yet to be demonstrated.

The first genetic evidence for a direct role of integrin in anchoring stem cells came from the study of follicle stem cells (FSCs) in the Drosophila ovary. In each ovariolo, there are a couple of FSCs reside in fixed regions at the top and bottom surface of the oval-shaped germarium (Fig. 1). The GSC niche at the anterior tip is believed to serve as the niche for FSCs as well. Hedgehog, Wingless and BMP ligands (Dpp and Gbb) are produced from the cap cells that function as long-range signals to control FSC maintenance and proliferation. Inner sheath cells, possibly along escort cells may contribute to the niche function by producing BMP and other signal molecules. DE-cadherin also contributes to the maintenance of FSCs by mediating cell adhesion

![Diagram showing the anatomic structures of the germline stem cell (GSC) niche and follicle stem cell (FSC) niche in the Drosophila ovary.](image)

**Figure 1.** A diagram showing the anatomic structures of the germline stem cell (GSC) niche and follicle stem cell (FSC) niche in the Drosophila ovary. Two GSCs (in orange) are located at the anterior tip of the germarium. They are anchored to the cap cells (in blue, the GSC niche) by forming homophilic adhesions between DE-cadherin expressing cap cells and DE-cadherin expressing GSCs (left inset). Two FSCs (in dark green) are located on opposite edges at the mid region of the germarium. They are anchored to the outer basement membrane by forming αβ integrin heterodimer-mediated adhesion between FSCs and the basement membrane (right inset).
between FSCs and neighboring inner sheath cells at the 2A/2B boundary.18 Strong DE-cadherin expressing foci were observed between the FSC and the inner sheath cell, which raises the possibility that these inner sheath cells might be stationary and do not belong to escort cells derived from escort stem cells at the anterior tip, as escort cells continuously get eliminated by cell death and replaced by new ones.36 FSCs also stably contact the basal lamina in maintaining the position of FSCs (Fig. 1).29 Firstly, integrin subunits, including αPS1 (encoded by mew), αPS2 (encoded by if) and βPS (encoded by mys) localize to the basal surface of the follicular epithelia. Notably, βPS and αPS1 have elevated levels at the posterior half of the gerarium, starting at the region where FSCs reside, suggesting a role in controlling FSCs. Secondly, those integrin subunits are required for FSC maintenance, as mys mutant FSCs frequently mislocalize to the center of the gerarium and differentiate, as a consequence of FSC detachment from the basal lamina. Interestingly, production of laminin A (lanA) by FSCs, the ligand for the αPS1 and βPS integrins, is required for FSC maintenance, suggesting a cell autonomous role of FSCs in assembling ECM to maintain themselves. This study also reveals a role of integrin in regulating FSC proliferation. mew, if and lanA mutant FSCs show normal positioning and morphology, yet their division rate has dramatically declined. These observations suggest that integrin mediated cell adhesion play two separable roles in the FSC niche: anchoring FSCs and promoting their proliferation. Integrins have been recently implicated in regulating spindle orientation in the monolayered follicular epithelium in the Drosophila ovary. mys mutant follicle cells at the poles of the egg chambers frequently become multi-layered as a result of spindle misorientation.37 It would be interesting to investigate the potential roles of integrins in anchoring and orientating mitotic spindles in epidermal niches for asymmetric stem cell divisions.

Another type of epithelial stem cells, intestinal stem cells (ISCs), have been identified in the Drosophila midgut.38,39 They are scattered along a thin layer of basement membrane of the gut epithelia composed of ECM, which separates ISCs from the surrounding circular muscles.38,39 Circular muscles produce Wingless niche signals to regulate ISC self-renewal, and thus constitute the ISC niche.40 In contrast to the fixed locations of FSCs in the gerarium, ISCs appear to have no apparent physical restriction for them to locate along the basement membrane. Integrin is also required for ISC attachment to the basement membrane, as mys mutant ISCs could not be maintained within the niche (Zhang and Xi R, unpublished data), indicating integrin-mediated cell adhesion as a general mechanism for stem cell anchorage in epidermal type of niches.

Integrin-mediated cell adhesion could also function indirectly to anchor stem cells. In the Drosophila male GSC niche, integrin-mediated cell adhesion anchors the hub (the GSC niche) to ECM at the anterior tip of the testis.41,42 While GSCs get attached to the hub by cadherin-mediated cell adhesion. Thus, similar to the FSC anchorage in the Drosophila ovary, both types of cell adhesion are required to locate GSCs in the Drosophila testis. These observations suggest that in niches where both cell-cell and cell-ECM contact are essential for maintaining stem cells, both types of cell adhesion could be utilized to anchor and secure stem cells in the niches (Fig. 2).

### Cell Adhesion Molecules in Mammalian Stem Cell Niches

The complexity associated with mammalian tissues makes it difficult to rigorously define the cellular makeup and anatomical structure of the stem cell niches. Among the best characterized stem cells, such as hair follicle stem cells in the skin, and hematopoietic stem cells in the bone marrow, specific adhesion molecules are found to be enriched in the stem cell population, which are also frequently used as one of the markers to distinguish stem cells with non-stem cells. Although functional evidence is limited, those observations suggest that similar adhesion mechanisms are utilized in mammalian stem cells for their anchorage in the niches.

There are two stem cell populations in the skin. One belongs to a subpopulation of keratinocytes that form a single cell layer and reside at the basal skin on the top of the basement membrane, which produces differentiating daughters that move upward to make the stratified epithelia. The other one, named hair follicle stem cell (HFSC), resides in a bulge structure beneath the sebaceous
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gland that gives rise to hair follicle and sebaceous gland. HFSCs also contribute to the regeneration of interfollicular epidermis during wound healing. Keratinocytes have enriched expression of integrins, including α6, β1 and β4 integrins. Knock-out either subunits in mice causes various extents of epidermal blistering, demonstrating their critical roles in epidermal adhesion to the basement membrane. The α3 integrin knock-out shows occasional epidermal blistering that is caused by rupture of the basement membrane, suggesting it is required for establishment and/or maintenance of basement membrane integrity, but not for adhesion between the epidermis and the basement membrane. Moreover, keratinocytes can be found in the suprabasal layers of the blistered epidermis, indicating that integrins likely play a similar role for stem cell adhesion to the basement membrane. HFSCs in the bulge can be divided into two populations based on α6 integrin expression levels. Those with high integrin levels are basal bulge cells that are directly attached to lamina, and those with low integrin levels are suprabasal bulge cells that are probably the immediate daughters of the basal bulge cells. The basal bulge cells appear to be less proliferative than the suprabasal bulge cells, suggesting that two populations of HFSCs represent quiescent and primed stem cells, respectively. These observations also indicate that integrin-mediated adhesion could play a negative role in HFSC proliferation. This is in contrast to proliferation-promoting activity of integrins in Drosophila FSCs, suggesting integrin could positively or negatively regulate stem cell proliferation depending on tissue context. In mouse fibroblast and epithelial cells, integrin is able to modulate cell proliferation by regulating PKB/AKT and GSK3 activities through integrin-linked kinase (ILK), and by cross-talking with epidermal growth factor receptor (EGFR) signaling, which have been reviewed in depth by others. It would be interesting to investigate whether similar mechanisms underlie integrin-mediated cell proliferation control in the stem cell niches.

HSCs in the bone marrow are believed to reside at two locations. One is the endosteum, the bone surface towards the marrow where osteoblasts and osteoclasts localize, and is known as the "osteoblastic niche." The other location is the surface of sinusoidal blood vessels, called "vascular niche." It is suggested that in the osteoblastic niche, HSCs anchor to the niche through homophilic adhesion between N-cadherin expressing HSCs and N-cadherin expressing osteoblasts. However, it is in debate whether N-cadherin is expressed in HSCs and whether it plays a role in HSC maintenance. A recent study shows that functional deletion of N-cadherin in HSCs does not affect HSC maintenance or their ability to reconstitute irradiated mice, demonstrating that N-cadherin is dispensable for HSC maintenance. It is possible that other cell adhesion molecules could compensate N-cadherin function for HSC anchorage in the osteoblastic niche. N-cadherin level in the HSCs is positively regulated by Angiopoietin-1 (Ang-1)/Tie2 signaling that is important for maintaining HSCs in a quiescent state, and negatively regulated by oxidative stress. Moreover, differentiating HSCs are accompanied by increased expression of c-Myc, which downregulates N-cadherin. Taken together, those observations indicate the existence of multiple regulatory mechanisms controlling cell adhesion and consequently HSC anchorage to and release from the niche in response to environmental signals.

Many adult stem cells are directly associated with or in proximity to the blood vessels, such as neural stem cells (NSCs) at the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone of the hippocampus, spermatogonial stem cells (SSCs) in the testis, and mesenchymal stem cells in a variety of tissues and organs. The vasculature environment may facilitate stem cell function by providing unique physical supports, compatible oxygen levels, and convenient access of instructive signals from bloodstream and endothelial cells. NSCs in the SVZ are also frequently associated with fractones, finger-like lamina structures that contacting the capillaries. Fractone may be an important component of the NSC niche, because it contains many ECM molecules in addition to perlecan, a N-sulfate heparan sulfate proteoglycan that is implicated in sequestering FGF-2 and possible other growth factors to control NSC behavior. NSCs in the SVZ express α6β1 integrins while the ligand laminin is expressed around the blood vessels. Disrupting integrin function by injecting neutralizing antibodies to the lateral ventricle of mice causes the release of NSCs from the vasculature and promotion of proliferation, suggesting that integrin facilitates NSC anchorage to the vascular niche and keeps NSCs in a quiescent state. The physical relationship between SSCs and vasculature, however, is not typical. SSCs and undifferentiated spermatogonia do not directly contact the vasculature. Instead, they are separated by interstitial cells and a layer of basement membrane of the seminiferous tubules. SSCs have enriched expression of α6β1 integrins, suggesting a role of integrin in attaching SSCs to the basement membrane. Isolated β1-integrin mutant SSCs are defective to recolonize the recipient testes after transplantation, suggesting integrin is also required during homing of SSCs to their niches.

Mammary stem cells (MaSCs) are located at the basal compartment of the mammary gland and can be isolated in part based on their high expression levels of β1 and α6 integrins. Each MaSC can develop into an entire functional mammary tree after transplantation with a fat pad, demonstrating its ability to generate a whole lineage. Targeted deletion of β1 integrin in the basal compartment compromises stem cell function, indicating a role of integrin in regulating MaSCs. One observation from above analysis of various tissue-specific stem cell niches is that α6β1 integrins seem to be the most common integrin heterodimers that function in the stem cell niches in diverse tissues. One exception is satellite stem cells, which primarily express α7 and β1 integrins. The tissue-specific stem cells discussed here and their expression of adhesion molecules are summarized in Table 1.

Summary and Perspective

In summary, cell-to-cell adhesion mediated by cadherin and other cadherin-like and immunoglobulin-like molecules and cell-ECM adhesion mediated by integrin are possibly two general mechanisms anchoring stem cells in the respective stromal and epidermal niches in diverse organisms. In addition, both types of cell adhesion molecules can be regulated by their interaction with the extracellular matrix and cell signaling pathways. The study of cell adhesion molecules in stem cell niches provides valuable insights into stem cell biology and may lead to the development of novel therapeutic strategies for stem cell transplantation and regeneration.
of cell adhesion could be utilized directly or indirectly in a single niche to robustly maintain stem cell anchorage in the niche (Fig. 2). The identification of adhesion molecules important for stem cell anchorage may help enhance our ability to deliver in vitro expanded stem cells to the correct niches in diseased tissues in future stem cell therapy. Apart from the function as cellular glue, adhesion molecules may also serve to anchor and orientate mitotic spindles for symmetric and asymmetric stem cell divisions, and mediate stem cell competition for niches. Moreover, these adhesion molecules form junctional structures and focal contacts that are dynamically regulated by multiple signaling pathways that control various cellular behaviors. They are also associated with many other ECM molecules and ligands, such as HSPGs and collagens that have been implicated in the sequestration or regulation of many important signal molecules.78,79 It is imaginable that these adhesion molecules and their associated structures in the stem cell niche provide an excellent platform to link stem cell anchorage and release with regulatory signals that are important for stem cell self-renewal, differentiation and turnover, whose deregulation may underlie many human diseases. With the rapid pace towards better elucidation of stem cell niche structure and function in diverse stem cell systems, new insights into the underlying mechanisms will continue to emerge.

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Table 1 Examples of tissue-specific stem cell niches with adhesion molecules in mouse

| Stem cell                          | Location                          | Niche contact                      | Adhesion molecules          | Recent references |
|------------------------------------|-----------------------------------|------------------------------------|-----------------------------|-------------------|
| Epidermal stem cells               | Basal layer of skin               | Basement membrane (BM)             | α6, β1 & β4 integrins       | 27, 80            |
| Hair follicle stem cells (reserved)| Bulge region of skin              | BM                                 | α5 integrin                | 50, 80            |
| Hematopoietic stem cells (reserved)| Endosteum                         | osteoblast                         | N-cadherin*                | 53                |
| Neural stem cells                  | SVZ                               | BM                                 | α6 β1 integrins            | 28, 62            |
| Spermatogonial stem cells          | Basal compartment at interstitium  | BM, Sertoli cell                   | α6 β1 integrins            | 67, 73, 74        |
| Mammary stem cells                 | Basal compartment                  | BM                                 | α5 β1 integrins            | 26, 75, 76        |
| Satellite muscle stem cells        | myofiber surface under basal lamina | BM, myogenic precursors            | α7 β1 integrins, M-cadherin* | 77                |

*Molecules that expressed in the niche but may have no requirement for stem cell maintenance and function.*75,81
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