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Cell adhesion in regulation of asymmetric stem cell division

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Abstract

Adult stem cells inevitably communicate with their cellular neighbors within the tissues they sustain. Indeed, such communication, particularly with components of the stem cell niche, is essential for many aspects of stem cell behavior, including the maintenance of stem cell identity and asymmetric cell division. Cell adhesion mediates this communication by placing stem cells in close proximity to the signaling source and by providing a polarity cue that orients stem cells. Here, I review the recent discovery that cell adhesion molecules govern the behavior of stem cells.

Introduction

Stem cells must be both maintained and held in check during long-term tissue homeostasis to prevent tissue degeneration or cancer. To strike this delicate balance, stem cells are carefully regulated according to the rate of consumption of differentiated cells. Stem cells reside in specialized anatomical locations, or niches, that support many aspects of stem cell identity, including an undifferentiated state, proliferation capacity, quiescence, and multipotency [1, 2]. In some systems, partially differentiated cells regain stem cell identity when placed back in the niche [3–6], suggesting that signaling within the niche dominantly controls stem cell identity.

Interactions between stem cells and their environment through cell-cell and cell-extracellular matrix (ECM) adhesion are crucial for regulating stem cells. Not only does adhesion help retain stem cells in the niche, where they receive essential signals, but it also provides polarity cues that help stem cells decide whether to divide symmetrically or asymmetrically [7]. Moreover, because signals from the niche are essential for stem cell identity, cell fate decisions are often associated with the polarization of stem cells, which retains the cells within or displaces them away from the niche. Indeed, orientation of the mitotic spindle regulates the fate of daughter cells in many types of stem cells [8]. Here, I review recent progress towards understanding how cell polarization orients the spindle in response to cell adhesion cues.

Cell adhesion in the organization of the stem cell niche

Both cadherins and integrins are required for stem cell-niche interactions in many systems. Among the most extensively studied stem cell niche systems are those in the *Drosophila* male and female gonads [9], in which E-cadherin is required for the attachment of germline stem cells (GSCs) to niche component cells.

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In the male gonad, GSCs are attached to hub cells, the major niche component, via E-cadherin-mediated cell adhesion [10,11] (Fig. 1A). N-cadherin is expressed in a similar pattern [12], but its functional significance has not yet been tested. Somatic cyst stem cells (CySCs, also known as cyst progenitor cells) also participate in the formation of the GSC niche and depend on E-cadherin to attach to hub cells.

Hub cells are also attached to the apical tip of the testis via integrin-mediated adhesion. The loss of β PS integrin results in a failure to position hub cells at the apical tip, leading to the loss of hub cells and subsequently of GSCs [13]. Since interaction among GSCs, CySCs and hub cells remains intact in the integrin mutants, the loss of hub cells detached from the apical tip may indicate that hub cells need extracellular signals, possibly from the apical tip ECM, for their maintenance [13]. While cell adhesion is required to maintain stem cells in the niche, the strength of adhesion must be tightly regulated to coordinate the production and regulation of multiple cell types needed to form a functional tissue. For example, CySCs can outcompete GSCs for niche occupancy when their integrin-dependent adhesion to the niche is inappropriately upregulated [14].

Similar to male GSCs, female GSCs are attached to cap cells in the niche via E-cadherin-mediated cell adhesion [15] (Fig. 1B). In the absence of E-cadherin, GSCs are quickly lost from the niche. Follicle stem cells (FSCs), which produce the follicle cells that form the egg chamber, also require E-cadherin [16,17] and α PS1/ β PS integrin [18] to be maintained in the niche. E-cadherin and integrin appear to function independently or in parallel during this process, since single mutants fail to efficiently maintain FSCs. Interestingly, FSCs that lack integrin are positioned abnormally within the germarium [18,19]. Since FSCs exhibit dynamic movements within the niche [19], E-cadherin and integrin may be required for adhesion to different substrata.

Together, these studies illustrate the importance of cadherins and integrins for organizing the geometry of the stem cell niche, and thus for maintaining stem cell identity.

Oriented stem cell division and cell-cell contact

Stem cells employ elegant cell biological mechanisms to divide asymmetrically. In *Drosophila* male GSCs, the mitotic spindles are oriented towards the hub cells (Fig. 2A) by stereotypical centrosome movement during interphase that positions the mother centrosome next to the hub and displaces the daughter centrosome away from the hub. EM data has shown that microtubules link the mother centrosome to the adherens junction at the hub-GSC interface [20]. Thus, it has been proposed that the adherens junction provides a polarity cue toward which the GSC orients [21]. However, the requirement of cadherins in spindle/centrosome orientation has not been formally proven due to the essential role of E-cadherin in cell adhesion: E-cadherin mutant GSCs are rapidly lost from the niche, leaving no GSCs to be assessed for their polarity.

Although integrins play an important role in organizing the stem cell niche [13], it is dispensable for interactions between the hub and GSCs or between hub cells. GSCs in integrin mutants can correctly orient their mitotic spindles toward the hub cells. Thus, cadherin and integrin play distinct roles in the *Drosophila* testicular niche.

In females, the GSC spindle is oriented toward the cap cells of the niche. However, unlike in males, the female GSC spindle is anchored to the spectrosome, a germline-specific organelle resembling the ER/Golgi [22](Fig. 2B). The spectrosome is located on the apical side of the GSC, next to the adherens junction between the cap cell and GSC. In the absence of the spectrosome, the spindle is not properly oriented. It is likely that the adherens junction provides the polarity cue, although this has not been formally proven. However, there is ample evidence that supports the involvement of cadherin in spindle orientation. For example, in the *Drosophila*

embryonic neuroepithelium, E-cadherin is required for epithelial cell organization and spindle orientation [23]. Similarly, in symmetrically dividing MDCK cells, E-cadherin is required for planar spindle orientation [24].

Regulation of spindle orientation in mammalian cells

As in *Drosophila*, many mammalian stem cells interact with neighboring cells or with the ECM via cadherins and integrins. Examples include neuronal stem cells, muscle stem cells, intestinal stem cells, spermatogonial stem cells, and hematopoietic stem cells (reviewed in [7]). Here, I will focus on stem cells whose spindle has been shown to be oriented with respect to the tissue architecture and discuss the role of cell adhesion in this process.

Skin stem cells

Basal epidermal cells, which function as skin stem cells during homeostasis, use spindle orientation to regulate asymmetric vs. symmetric divisions. Basal epidermal cells attach to the basement membrane via hemidesmosomes ($\alpha 6 \beta 4$ integrins) and focal adhesions ($\alpha 3 \beta 1$ integrins) [25] (Fig. 3A). The basement membrane provides essential growth factors and ECM molecules, including laminin 5, fibronectin, collagen IV, TGF α , and IGFs, to maintain the stem cell identity of basal epidermal cells [25]. Since attachment to the basement membrane is key for stem cell identity, perpendicular vs. parallel spindle orientation with respect to the basement membrane results in asymmetric vs. symmetric stem cell division, respectively [26]. In the embryonic epidermis of $\beta 1$ -integrin or α -catenin null mice, basal epidermal cells lose their polarity and misorient their spindles, demonstrating the importance of focal adhesions and adherens junctions in stem cell polarity and oriented divisions [26]. However, in the adult mouse epidermis, perpendicular spindle orientation is observed in only ~3% of cells, which is too small a fraction to account for the asymmetric divisions in this tissue [27]. Thus, alternative mechanisms might exist to achieve the asymmetric stem cell division in this system.

Muscle satellite cells

Satellite cells are located between the basal membrane and the plasma membrane of the muscle fiber and are composed of a mixture of stem cells and myogenically-committed cells. $\alpha 7 \beta 1$ integrins are localized to the basal membrane of the satellite cell, while M-cadherin is at the other side facing the muscle fiber [28–30] (Fig. 3B). Within this niche, Pax7+Myf5- stem cells can divide symmetrically, or asymmetrically to produce a self-renewing stem cell and a myogenically-committed cell. Based on the position of the daughter cells of a satellite cell division, it has been proposed that planar division (division axis parallel to the basal membrane and muscle fiber) results in symmetric division, while apical-basal division (division axis perpendicular to the basal membrane and the muscle fiber) results in asymmetric stem cell division [31]. Thus, it is plausible that the mitotic spindle is oriented with respect to the axis, although dividing satellite cells have not been directly observed. Interestingly, in cultured mitotic myoblasts, multiple fate determinants, including Numb [32,33], Desmin, and Sca-1 [34], are segregated asymmetrically. Although it is tempting to speculate that stem cells divide asymmetrically by orienting their mitotic spindles to coordinate the polarity of intrinsic fate determinants with extrinsic niche polarity, further studies are needed to test this idea.

Neural stem cells

During the development of the rodent central nervous system, neuroepithelial cells, which divide symmetrically before the onset of neurogenesis, and radial glia progenitors, which divide asymmetrically after the onset of neurogenesis, serve as neural stem cells. These cells are polarized along the apical-basal axis, with the apical process facing the ventricular surface and the basal process facing the pial surface [35,36]. Although the spindles of asymmetrically

dividing radial glia progenitors are roughly parallel to the apical surface [35,37] (Fig. 3C), slight tilting of the spindle axis can result in asymmetric inheritance of a very tiny apical cell surface [35]. The apical surface of these neural stem cells contains adherens junctions and polarity proteins, including Par3 and aPKC [38,39], and the inheritance of this apical surface has been proposed to determine stem cell fate [37,38]. A recent study suggested that Par3 is asymmetrically localized during radial glial progenitor mitosis, and that Par3 regulates asymmetric fate via regulation of Notch signaling, indicating a more direct role of Par3 in fate determination [40]. Spindle orientation in neural stem cells is regulated by an evolutionarily conserved mechanism requiring LGN [37] and Strabismus/Vangl2 [41], and regulates the inheritance of the apical membrane domain. Recent work has shown that during asymmetric division, the radial glial progenitor cell retains the mother centrosome, while the differentiating daughter cell inherits the daughter centrosome [42] (Fig. 3C), highly reminiscent of what occurs in *Drosophila* male GSCs [20].

In addition to cadherin and polarity proteins, integrins are also strongly expressed by neural stem cells. $\beta 1$ integrin and laminin $\alpha 2$ at the apical ventricular zone surface play critical roles in the maintenance of neural stem cells within the niche and proper spindle orientation [43]. Other integrins implicated in neural stem cell function [44–47] have not been tested for potential roles in spindle orientation.

Intestinal stem cells

Recently, intestinal stem cells were reported to have stereotypical orientation with respect to the tissue architecture. The spindles of intestinal stem cells are oriented perpendicular to the apical cell surface (towards the lumen of the crypt)[48] (Fig. 3D), while transit-amplifying progeny of stem cells appear to orient their spindles parallel to the lumen [49]. Interestingly, the tumor suppressor Apc (adenomatous polyposis coli) is essential for correct spindle orientation in both intestinal stem cells and transit-amplifying cells. Given that inactivation of Apc in the stem cell compartment is critical for tumor formation [50], it is tempting to speculate that loss of asymmetric stem cell division plays a crucial role in tumorigenesis. However, more work must be done to determine how stereotypical spindle orientation leads to potentially asymmetric stem cell division, and the identity and source of signals that together with spindle orientation achieve asymmetric stem cell division.

Conclusion

Cell adhesion molecules play versatile roles in stem cell function, providing an anchor for stem cells to the niche, a platform for stem cell-niche signaling, and a polarity cue for orientation of stem cell mitotic spindles. Yet, these different roles of cell adhesion molecules stem from a common molecular function: connecting the surface of the stem cell to the outside environment. Moreover, since cell adhesion molecules are not limited to stem cells, an intriguing possibility is that the regulation of these molecules, including their choice of partner molecules, is linked to cell fate determination mechanisms. Future studies will provide insights into how stem cell-specific programs regulate cell adhesion properties to carry out cell biological processes specific to stem cells.

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Figure 1. The anatomy of *Drosophila* male and female germline stem cell niches and the role of adhesion molecules

A) In the testis, the major stem cell niche component, hub cells, attach to the apical tip of the testis via integrin, while hub-GSC and hub-cyst stem cell (CySC) attachment are supported via adherens junctions. CySCs encapsulate GSCs and create a niche for them together with hub cells. After stem cell division, GSCs produce a differentiating daughter, or gonialblast (GB), while CySC produce cyst cells (CCs), which encapsulate and promote differentiation of germ cells (GB and spermatogonia).

B) In the ovary, GSCs are attached to cap cells (in proximity to terminal filament (TF) cells) via adherens junctions. GSCs are encapsulated by escort stem cells (ESCs), which produce escort cells (ECs) that accompany differentiating germ cells (cystoblast (CB) and cystocytes). Follicle stem cells (FSCs), which produce the follicle cells (FCs) that create the egg chamber, are maintained by both cadherin and integrin function.

Figure 2. Regulation of asymmetric stem cell division in *Drosophila* germline stem cells

Asymmetric stem cell divisions of *Drosophila* male (A) and female (B) GSCs. In both GSCs, the mitotic spindles are oriented toward the adherens junction formed between the GSC and the niche component cells (hub or cap cells). In males, the mother centrosome is consistently oriented toward the adherens junction, while in females, the spectroosome is consistently anchored near the adherens junction.

Figure 3. Cell adhesion and spindle orientation during mammalian stem cell divisions

Asymmetric division of skin stem cells (A), satellite cells (B), neuronal stem cells (C), and intestinal stem cells (D). Known components of the stem cell niche and participating adhesion molecules are illustrated. For satellite cells (B), direct observation of spindle orientation relative to the muscle fiber and/or basement membrane has not been performed. In neuronal stem cells (C), the mother centrosome is consistently inherited by stem cells, similar to *Drosophila* male GSCs. In intestinal stem cells (D), the spindle is oriented perpendicular to the crypt lumen, while transit-amplifying daughters orient their spindles parallel to the surface of the lumen.