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Review

Stem cell decisions: A twist of fate or a niche market?

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ABSTRACT

Establishing and maintaining cell fate in the right place at the right time is a key requirement for normal tissue maintenance. Stem cells are at the core of this process. Understanding how stem cells balance self-renewal and production of differentiating cells is key for understanding the defects that underpin many diseases. Both, external cues from the environment and cell intrinsic mechanisms can control the outcome of stem cell division. The role of the orientation of stem cell division has emerged as an important mechanism for specifying cell fate decisions. Although, the alignment of cell divisions can dependent on spatial cues from the environment, maintaining stemness is not always linked to positioning of stem cells in a particular microenvironment or 'niche'. Alternate mechanisms that could contribute to cellular memory include differential segregation of centrosomes in asymmetrically dividing cells.

Contents

1. Introduction

One of the central questions in cell and developmental biology is how differences in cells are established and maintained. In multicellular organisms this problem is not restricted to development but is also relevant during tissue homeostasis in the adult. One mechanism for establishing different cell fates is asymmetric cell division. In this context, the transmission of cell fate information can occur through cell–cell communication, it can be established *via* intracellular polarity or it can be inherited from one cell generation to the next [1]. Stem cells are one cell type that can divide asymmetrically to produce a self-renewed stem cell and a daughter cell that will differentiate. Stem cells can also divide symmetrically to expand the stem cell pool. Increasing stem cell numbers or generating differentiating cells is a key process in building and maintaining tissues. In the context of stem cells the orientation of the mitotic spindle can influence the fate of daughter cells [1,2]. The correct alignment of mitotic spindles is not only important in development but defects in this process are also associated

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with disease [3,4]. It is thus not surprising that controlling the orientation of mitosis is an important issue for tissue morphogenesis [5–7]. The different requirements and contexts in which stem cells are found predict that a plethora of regulatory mechanisms operate to govern spindle orientation and cell fate decisions. Here we discuss intrinsic and extrinsic cues that are involved in asymmetric stem cell division and focus specifically on the contribution of selective centrosome segregation.

1.1. Principle concepts of spindle orientation

Invertebrate model systems have proven extremely useful for unraveling the general principles that underpin spindle orientation during asymmetric cell division. The genetic approaches possible in these model systems permit asking detailed questions about this process. They also enable identification and easy access of the cells under investigation. Importantly, most of the molecular principles of asymmetric division identified in *Drosophila* and *Caenorhabditis elegans* are highly conserved [1,8,9].

How is spindle orientation achieved? A series of events cooperate to position the spindle. In many instances two key events are required that are tightly coupled (Fig. 1). First, cell polarity needs to be established specifying cortical regions that can capture the spindle. Second, the spindle apparatus needs to be able to interact with the cortex. Typically, astral microtubules nucleated by centrosomes at the spindle poles serve this purpose. Common to this process in various contexts, is the contribution of a conserved, sophisticated molecular machinery that includes cortical and microtubule binding proteins in addition to molecular motors that can exert torque on the spindle. Our understanding of the key molecules involved in this machinery is steadily increasing [10].

In Brief, G alphai, LGN (ASG3 in *C. elegans* and Pins in *Drosophila*) and Numa (Lin-5 in *C. elegans*, Mud in *Drosophila*) constitute the conserved core set of molecules involved in spindle positioning (Fig. 1). G alphai can be myristoylated and binds to the cortex [11]. G alphai also regulates the activity of Pins by increasing its affinity for Mud [12]. Pins/LGN binds Mud/Numa [2,13–15]. In turn, Numa/Mud can interact with cytoplasmic Dynein [16,17], which can exert forces to orient the spindle. Hence, this protein complex can function in anchoring and positioning the spindle. These molecules also play important roles in directing spindle orientation in progenitor cells in the mouse neocortex, the chicken neural tube, and during symmetric divisions in developing epithelia [18–22]. The proteins involved seem to function similarly in different contexts. Nonetheless, how the orientation of mitotic spindles influences the outcome of progenitor/stem cell division varies and is not understood in many progenitor cells [23]. Another difficulty is that measuring spindle orientation reliably in complex stratified vertebrate tissues is more complex than in the simpler tissue structures of *Drosophila* or *C. elegans*.

1.2. Spindle orientation – how to measure it properly?

In vertebrates, the orientation of mitotic spindles is commonly used to classify symmetric and asymmetric divisions [24–27]. Although the position of daughter cells does not necessarily predict the fate of resulting daughter cells, the alignment of mitotic spindles perpendicular to the tissue layer in which the mother resides, usually this corresponds to the apical surface, is considered asymmetric because the daughter cells inherit different proportions of apical polarity markers. The problem that arises especially in morphologically complex tissues is: what is used as reference to determine the orientation of the spindle? It is important to note that the methods used to measure mitotic spindle alignment have never been compared directly and the reference points used to report the angle of spindle orientation differ between investigators and systems [24–27]. This may explain discrepancies between observations in the same system [24–27]. In tissue that is curved like the base of the intestinal crypt, it becomes even more difficult to define relevant reference points or axes that relate to cell or tissue organization and more robust methods for these measurements in three-dimensional tissue are needed.

1.3. Stem cell compartment, plasticity and the niche concept

Additional complexity is added by the emerging view that at least some stem cell compartments have a high degree of plasticity. Within some tissues, several cell populations can act as stem cells in a context dependent manner. Which stem cell pool is the active one under a given set of circumstances? This important for understanding the role of spindle orientation in cell fate decisions and is particularly relevant in the stem cell compartment of the mouse intestine. In recent years much progress in understanding the biology of the stem cells at the base of intestine has been made revealing a high level of plasticity within this compartment [28].

Leucine-rich repeat containing G protein-coupled receptor 5 (LGR5) was identified as a marker of cells that can generate all the lineages normally present in the intestinal epithelium [29]. Within the epithelium, Paneth cells are secretory cells that are usually restricted to the crypt base where the antimicrobial peptides they secrete are thought to protect neighboring stem cells [30]. Previously, cells that reside at position +4, above the last Paneth cell, were identified as stem cells based on their ability to retain labeled DNA [31]. These so called +4 cells express low levels of LGR5 in addition to the marker Bmi1. Importantly, +4 cells can restore $LGR5^{Hi}$ cells upon their depletion [32]. Similarly when +4 cells are specifically depleted, they are restored from the $LGR5^{Hi}$ pool [33]. To complicate the situation further, a subset of Paneth cells can act as reserve stem cell pool when called upon in response to injury or disease [34]. Together these and other similar observations illustrate the high degree of plasticity that exists in this tissue between different pools of progenitor cells in this tissue. The high turn over of cells in the intestine makes it vital to maintain a constant supply of replacement cells. A highly dynamic stem cell compartment that includes back-up provisions ensures the survival of the organism. The molecular mechanisms that control these decisions remain a mystery but they are likely to include a complex interplay between different signaling pathways, differential adhesion between cells and basement membrane, and mechanical forces that act at the level of cells and tissue.

Stem cells usually reside in a particular environment called the niche, that hosts and maintains stem cells [35,36]. One idea that has gained popularity is that the niche is the dominant factor in controlling stem cell fate by providing short-range signals that confer stemness on cells within their range. In the *Drosophila* germline, niche signals can even promote reversion of cells that are partially differentiated to become stem cells again [37,38]. However, such powerful effects of the niche are not universal. In the case of the hair follicle, cells do not revert to a stem cell fate when they return to the niche after exiting and differentiating even when the niche is depleted of endogenous stem cells [39]. On the other hand, hematopoietic stem cells can leave the niche without loosing their stemness [40] and neural stem cells can exist and symmetrically self-renew outside their complex microenvironment [41].

In the case of the crypts in the intestine, Paneth cells secret important stem cell maintenance factors including Wnt [42]. If Paneth cells are experimentally ablated, however, stem cells are maintained *in vivo* [43]. Hence crypt stem cells have the capacity to compensate for the loss of Paneth cells and maintain stemness by other means. Similarly, murine neuroepithelial progenitor cells removed from their normal location produce neurons at normal frequency suggesting that their self-renewal capacity does

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