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Editorial

# Molecular Control of the Mode of Cell Division: A View from Mammalian Lung Epithelial Stem Cells

**John Ku and Ahmed H. El-Hashash***
Stem Cells, Regenerative Medicine and Developmental Biology Program, University of Southern California, USA

***Corresponding author:** Ahmed H. El-Hashash, Stem Cells, Regenerative Medicine and Developmental Biology Program, University of Southern California, Los Angeles, USA

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## Editorial

Proper control of epithelial stem cells is essential for development of mammalian lung [1,2]. In the lung, congenital defects of stem cells lead to the development of different types of fetal abnormalities, including Broncho Pulmonary Dysplasia (BPD) and lung hypoplasia by several affecting critical processes such as the capacity of gas diffusion [1,2–4]. Balancing self-renewal and differentiation of tissue-specific stem cells is crucial to maintain tissue homeostasis of different organs such as the lung. Excessive stem cell self-renewal may result in tissue hyperplasia and/or tumorigenesis, while increased cell differentiation may lead to tissue degeneration and/or aging. Understanding the molecular mechanism that regulate the balance between stem cells proliferation and differentiation in the lung will lead to identifying new solutions to both restore lung morphogenesis and repair of the gas diffusion surface. Studies in my laboratory have shown that asymmetric cell division is critical for proper balance between self-renewal and differentiation of lung-specific stem cells during development [5-7], and for proper temporal and spatial specification of epithelial cell lineages [8,9]. Several studies on the lung have demonstrated that homogenous growth of stem cells take places due to different fates of symmetric and asymmetric cell division, which they undergo [10,11]. There are several ways that can be used to differentiate between symmetric and asymmetric division, including spindle orientation and differences in inheritance of the cell fate determinant [12–16]. Microenvironment, in which each daughter cell is placed in different microenvironment and therefore, undergoes different fate, represents an example of extrinsic fat determinants that result in division of the stem cells. On the contrary, cytoplasmic cell fate determinants such as Numb represent an example of intrinsic fate determinants that is important for asymmetric stem cell division. For instance, preferential segregation of the cell fate determinant Numb into one of the daughter cells controls asymmetric stem cell division in Drosophila and mammalian epithelial cells [17,18]. In Drosophila, C. elegans and vertebrates, both definition of the axis of polarity and asymmetrical localization of cell fate determinants in the dividing cells are key processes in determining the apical basal orientation and allowing a rapid switch from proliferation to differentiation [17]. During interphase, the cell fate determinant Numb is expressed uniformly in the cell, while during cell division it has an asymmetric cytoplasmic localization, and then segregates to one of the two daughter cells. High Numb level functions to suppress Notch activity in the cell and, therefore, induces cell differentiation. On the contrary, cells that have low Numb levels preserve high Notch activity and, therefore, acquire stem cell fate [19–22]. Studies carried out in our laboratory have shown that asymmetric distribution of Numb at the apical side of epithelial stem cell is for triggering asymmetric cell division in the embryonic lung [15,16]. We have also identified a positive correlation between perpendicular asymmetric cell division and segregation of the cell fate determinant Numb to one daughter cell, suggesting that epithelial stem cells divide asymmetrically in the lung [16]. Cell polarity depends on the asymmetric localization of certain cellular components within a single cell. Both orientation of mitotic spindle and cell polarity play an important aspects of epithelial cell behavior such as self-renewal and differentiation. They can also affect various physiological processes within the epithelial cell, including differentiation and branching morphogenesis. Intensive studies in our laboratory have provided evidences that distal epithelial stem and progenitor cells are polarized, highly mitotic and divide perpendicularly in the embryonic lung [23,15,16]. Our studies have also demonstrated that cell polarity contributes to both organization and integration of complex molecular signaling, and therefore, can help lung epithelial stem/progenitor cells to decide their fate, proliferation and differentiation [5,15,16]. For instance, we found that cell polarity plays role in the perpendicular division of lung stem cells, and disruption of lung stem cell polarity leads to loss of the balance between self-renewal and differentiation in culture [5,15,16]. In addition, our research on the asymmetric localization of proteins controlling spindle orientation such as mouse Inscuteable (mInsc), G-Protein Signaling Modulator 2 (GPSM2), and Nuclear Mitotic Apparatus (NuMA) polarity proteins has provided evidences of the correlation between perpendicular cell division and asymmetric cell division in mitotic lung epithelial stem cells [5,15,16,24], which has been previously reported in epithelial cells of different mammals [25]. Apical-basal polarity is one of the characteristic of epithelial cells in various organs. Subtle deviation of the spindle orientation in dividing epithelial cells leads to an asymmetrical distribution of both their apical plasma membrane and adjacent adherent junctions to the daughter cells. This mostly results in the switch from symmetric to asymmetric division in epithelial cells [26,27]. The cell-cell adhesion molecule E-cadherin is a component of both apicolateral junction complex and lateral epithelial cell plasma membrane [28]. We and others have demonstrated that the plasma membrane shows the 'Cadherin hole' as a comparatively small, unstained segment in the cell surface of mitotically dividing lung stem/progenitor epithelial cells and neuroepithelial cells by immunostaining of E-cadherin [16,24,27]. It is well established that the orientation of the cleavage plane relative to the cadherin hole in dividing epithelial cells can predict whether symmetric or asymmetric distribution of the plasma membrane to




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daughter cells occurs in different organs [27]. We carried out intensive analysis of the cadherin hole in dividing distal lung epithelial stem cells, and found that most of these stem cells divide asymmetrically; with their cleavage planes are predicted to bypass the cadherin hole, resulting in asymmetric distribution of the cadherin hole to their daughter cells [16,24]. In addition, studies in our laboratory have demonstrated that Eya1 protein phosphatase plays a critical role in the regulation of cell polarity, spindle orientation and asymmetric distribution of the cell fate determinant Numb in dividing lung epithelial stem/progenitor cells [5,24]. Eya1 phosphatase is highly expressed in lung epithelial cells, and stimulates both perpendicular cell division and asymmetric segregation of Numb to one of the two daughter cells during cell division by regulating the phosphorylation level/activity of the polarity protein aPKCζ [5,24]. Interfering with Eya1function *in vivo* or *in vitro* leads to defects in both cell polarity and mitotic spindle orientation of dividing lung epithelial stem/progenitor cells [5]. Thus, Eya1 deletion leads to disruption of perpendicular division and inheritance of Numb, which is an inhibitor of Notch signaling, by the two daughter cells, leading to inactivation of Notch signaling in these daughters of dividing lung epithelial stem/progenitor cells [5]. Eya1 deletion, therefore, leads to increased symmetric cell division, with increased differentiation, but reduced self-renewal of epithelial stem/progenitor cells in the lung. Since maintenance of the balance between stem cell self-renewal and differentiation is needed for normal lung morphogenesis and repair [1,2], our novel discovery about the crucial role of Eya1 phosphatase in balancing self-renewal with differentiation will help to understand premature or injured lung and possible postnatal respiratory distress, which may result from deficiency of this balance. These findings from our laboratory provide a framework for future translationally oriented studies in this area. Further investigation and uncovering of the underlying molecular mechanisms that control asymmetric division in lung stem/progenitor cells can help in identifying novel targets for prevention and rescuing lethal lung diseases in both human infants and children, and for regeneration of injured lungs.

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