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Editorial

New Insights Into the Regulation and Functional Significance of Numb in Lung Stem Cells During Organogenesis

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The cell fate determinant Numb is a crucial determinant of asymmetric versus symmetric cell division reviewed in [1,2]. The protein Numb is coded for by the gene, *NUMB,* which has an apparently evolutionarily conserved mechanism and function [3]. Numb protein controls binary cell fate decisions during organogenesis in different systems, including the peripheral and central nervous systems of both invertebrates and mammals [4].

Numb expression and function during development have been comparatively well studied in *Drosophila* and the mammalian nervous system [5]. It plays an essential functional role in asymmetrical cell division (ACD) during organogenesis by allowing for differential cell fate specification mitotic cells.

In both *Drosophila* and mammalian epithelial cells, ACD is mediated by preferential segregation of intrinsic cell fate determinants such as Numb into one of two sibling daughter cells. In these systems, numb is asymmetrically localized in mitotic cells, in which it defines the axis of polarity that will determine the orientation of the apical-basal cell division plane. This pattern of numb localization allows a rapid switch from proliferation, wherein two similar daughter cells are born, to diversification, wherein different-shaped daughter cells are generated [5]. During cell division, Numb has a polarized localization at one end of the stem/progenitor cell and subsequently segregates asymmetrically to only one daughter cell where it determines cell fate intrinsically [4]. Numb protein signaling, therefore, plays an essential functional role in binary cell fate decisions following ACDs

Numb protein functions as a Notch signaling inhibitor and is expressed uniformly in the cytoplasm in interphase but is localized asymmetrically in dividing cells. Hence, numb is asymmetrically segregated and inherited by one daughter cell only, enabling this cell to adopt a different fate from that of its sibling. The daughter cell that receives high levels of numb suppresses extrinsic Notch signaling and differentiates, whereas the daughter cell with low numb levels will normally maintain high notch activity and thus has a stem cell fate [6,7]. Similarly, numb normally localizes to one side of the mitotic mother cell such that it is segregated and inherited selectively by one daughter cell during neurogenesis. This asymmetric segregation and inheritance allows a daughter cell containing numb to acquire a different fate than the other daughter cell that does not inherit numb. In addition to its functional role in in binary cell fate decisions, Numb has also been shown to play a role in tumorigenesis and neural progenitor cell migration [4].

In mammals, four isoforms of Numb protein are expressed, whereas only one form of Numb exists in *Drosophila*. There is also a Numb homolog called "Numb-like," or NUMBL. Numb protein has a phosphotyrosine-binding (PTB) domain and a C-terminal region that has both a conserved binding motifs for α-Adaptin and Eps15 homology (EH) domain containing proteins. In contrast to Drosophila Numb, mammalian Numb proteins are not as well understood.

In mammals, control of epithelial stem/progenitor cells is essential for correct development of the lung [8,9]. In the lung, lethal defects of gas diffusion capacity such as the common congenital forms of lung hypoplasia and bronchopulmonary dysplasia (BPD) as well as the limited capacity of the lung to recover from them could be explained by a significant deficiency of stem or progenitor cells [10-12]. Understanding how to achieve a proper balance between different fates of lung-specific stem/progenitor cells, including the balance between self-renewal and differentiation could, therefore, provide innovative solutions to restoring normal lung morphogenesis and possibly regeneration of the gas diffusion surface. Asymmetric cell division (ACD) during development is indeed a critical mechanism that maintains the balance between self-renewal and differentiation as well as correct spatial and temporal specification of cell lineages in epithelial cells [1,2,13].

Recent studies in our laboratory have shown that distal lung epithelial stem cells are polarized, with perpendicular rather than parallel divisions [14,15]. In these stem cells, Numb show polarized apical localization [15,16]. In addition, we have identified the temporo-spatial and proximal-distal expression pattern of Numb during lung morphogenesis, which is significant for the understanding of asymmetric cell division in both proximal and distal lung epithelial stem cells. Our studies have demonstrated very weak expression levels of Numb in the distal lung epithelial stem cells during early lung morphogenesis (at E11.5–12.5). Later on, Numb expression levels increase in the distal rather than proximal lung epithelium [16]. We have also reported that both Numb and Numb-associated signal α-Adaptin are asymmetrically distributed and highly concentrated at the apical side of distal epithelial stem cells, with little or no staining at the basal pole [16]. α-Adaptin is an endocytic protein that is required for Numb-mediated ACD [17]. In addition, we reported that Numb is

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segregated to and inherited by one daughter cell in most mitotic stem/progenitor cells of lung distal epithelium [14]. We have, therefore, concluded that the more perpendicular/asymmetric cell division is, the more likely it is to segregate Numb preferentially to one daughter cell in mitotic lung epithelial stem cells, which strongly suggest ACD in distal epithelial stem cells of embryonic lungs [16].

Several studies have shown that Numb influences cell fate by inhibiting Notch signaling activity through polarized receptor-mediated endocytosis. Notch signaling promotes stem cell identity at the expense of differentiated cell phenotypes in different systems. Mechanistically, Numb acts as a linker between Notch and α-Adaptin, which functions to facilitate the endycytosis of Notch [18]. Prior to mitosis, Numb is expressed uniformly in the cytoplasm during interphase, but is localized asymmetrically in dividing cells. Hence, Numb is inherited by only one daughter cell, enabling this cell to adopt a different fate from that of its sibling. Consequently, the cell with low Numb levels maintains high Notch activity and thus has a stem cell fate whereas; the cell receiving high levels of Numb suppresses extrinsic Notch signaling and differentiates [6,7,19,20,13]. Our studies in the lung epithelial stem cells have shown that knocking down Numb enhances Notch signaling activity, in combination with a significant increase of the number of stem cells. This supports Numb functions as a cell fate determinant, and suggests a conserved function for Numb in controlling Notch1 signaling in the lung [16].

Furthermore, recent studies in our laboratory have shown that *Eya1* protein phosphatase regulates cell polarity, and the asymmetric polarized localization of Numb in lung distal epithelial cells [15]. These studies have provided several evidences that *Eya1* phosphatase stimulates both perpendicular division and Numb asymmetric segregation to one daughter in mitotic distal lung epithelial stem cells, probably by the regulation of aPKCζ phosphorylation levels [15]. Consequently, perpendicular division is not maintained and Numb is segregated to both daughter cells in mitotic epithelial cells, which leading to inactivation of Notch signaling after *Eya1* deletion in lung epithelial stem cells [15].

The detailed functions of Numb in the lung stem cell fate remain largely unexplored. In this regard, our recent studies [14-16] are to be commended for showing for the first time that Numb is critical for lung stem cell fate. These studies also suggest that important steps forward in our understanding of lung development, repair and regeneration can be achieved through more investigations of the mechanisms of Numb functional activities in lung stem cells.

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