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Protein phosphatase regulation of apical-basal polarity: A new mechanism for lung stem cell behavior and protection against lung fibrosis

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The balance between cell gain (self-renewal) and cell loss (apoptosis and differentiation) governs the size of the progenitors' compartment. Molecular programs regulating the balance between the self-renewal and differentiation and the balance of apoptosis versus self-renewal/differentiation of endogenous organ-specific stem/progenitor cells are likely critical both to the development and to regenerating diseased and damaged tissues in different organs, including the lung. Recent studies demonstrated the importance of disruption of epithelial apical-basal polarity (mediated by Par- polarity protein complex) in epithelial cell apoptosis and proliferation. However, how epithelial polarity regulation is coupled with apoptosis and proliferation is not well understood. We find that Asp-based PTPs such as Eya1 and none-receptor PTPs are essential for balancing differentiation and proliferation, and apoptosis versus self-renewal/differentiation, respectively by controlling the activity and localization of Par polarity complex in lung distal epithelial progenitors. The difference of the effect of these different PTPs possibly reflects the facts they regulate the activity and localization of Par polarity complex by targeting the activity of different upstream signaling events: Eya1 controls Par polarity complex by binding to and controlling aPKCζ activity, while none receptor PTPs controls Par complex by controlling the activity of Rho GTPases. Thus, Eya1 phosphatase regulates cell polarity and mitotic spindle orientation by controlling aPKCζ phosphorylation levels. Loss of apical-basal polarity in Eya1-/- distal lung progenitors results in loss of asymmetric cell division, leading to increased symmetric differentiation and hence lack of stem/progenitor cell self-renewal. Conversely, none-receptor PTPs control Par complex by regulation of the activity of Rho GTPases. Conditional deletion of none-receptor PTPs in lung epithelial progenitors results in disruption of Par polarity complex, and consequently inhibition of PI3K pathway leading to activation of the caspase-3 apoptotic cascade that results in increased apoptosis, but decreased cell proliferation/differentiation. Most importantly, we find that these mechanisms are recapitulated during fibrosis in alveolar epithelia undergoing apoptosis, which is a crucial early step in the development of lung fibrosis

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