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# Stem cell behavior in development and regeneration: To balance or imbalance

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A defining feature of stem cells is their ability to continuously maintain a stem cell population (i.e. self-renew) while generating differentiated progeny. Both embryonic and tissue-specific stem cells are faced with a uniquely difficult task: to avoid cell cycle exit and differentiation, and to avoid uncontrolled proliferation and tumor formation. Therefore, stem cells are required to maintain a proper balance between cell gain (self-renewal) and cell loss (apoptosis or differentiation). Loss of this balance leads to severe developmental defects and adult diseases, including cancer and fibrosis, all of which are highly costly and morbid medical conditions. How stem cells walk this developmental tightrope is an extremely interesting question that is of relevance to our understanding of the processes of cell differentiation and cancer, and of the developmental diseases that result from the premature loss of stem cell pools. 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 cells are likely critical both to development and to regenerating diseased and damaged tissues. Recent studies from our laboratory have identified the importance and molecular mechanisms of several transcription factors and protein phosphatases in balancing self-renewal versus differentiation or self-renewal versus apoptosis of tissue-specific stem cells. Using the lung as a model organ, we discovered that two classes of protein phosphatases (PTPs): Asp-based PTPs and non-receptor PTPs are essential for balancing self-renewal versus differentiation, as well as self-renewal versus apoptosis, respectively, of lung-specific stem cell during embryonic and adult stages. These enzymes do this by controlling the activity of the Par polarity complex and Notch1 signaling activity. Conditional genetic deletion of Asp-based PTPs in murine lungs results in loss of the balance between self-renewal and differentiation of lung-specific stem cells, leading to lung hypoplasia in mice. Conversely, conditional genetic deletion of non-receptor PTPs results in loss of the balance between self-renewal and apoptosis of these stem cells, leading to lung hypoplasia during embryogenesis or pulmonary fibrosis in adult mice. This imbalance between self-renewal and differentiation or apoptosis can be restored by intratracheal administration of these phosphatases or by genetic activation of downstream signal pathways such as Notch1, which leads to alleviations of lung hypoplasia during embryogenesis as well as reversing of pulmonary fibrosis in adult mice. These novel findings signify that PTP deficiency-mediated fibrosis is a feasible therapeutic target. They will also help in devising new therapeutic approaches to understand and eventually correct pulmonary fibrosis that is a lethal disease affecting 5 million people world-wide, with an average survival of 2-3 years following diagnosis and without an approved-treatment till now.

## Biography

Ahmed HK El-Hashash has completed his PhD from Manchester University, UK and postdoctoral studies from Mount Sinai School of Medicine of New York University and Children's Hospital Los Angeles. He is currently Assistant Professor of Stem Cell Biology and Regenerative Medicine at Keck School of Medicine and Ostrow School of Dentistry of University of Southern California. He has published more than 20 papers in reputed journals and serving as an editorial board member of repute.

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