LS-BK SEMINAR

"Friend or Foe: Inflammation in tissue regeneration during injury repair"

Jinwook Choi

Wellcome-MRC Stem Cell Institute, University of Cambridge

- **Date: 4:00PM, September 30(Thursday), 2021**
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- **Inquiry: Prof. Seung-Woo Lee (279-2355)**
- **Abstract:**

Tissue regeneration is a multi-step process mediated by diverse cellular hierarchies and states that are also implicated in tissue dysfunction and pathogenesis. Alveolar type 2 (AT2) cells function as stem cells by self-renewing and differentiating into alveolar type 1 (AT1) cells that are essential for gas-exchange in the lung. However, how AT2 cells are activated from the quiescence and which trajectory they follow to differentiate into AT1 cells remain unknown. Here, we leveraged single-cell RNA sequencing in combination with *in vivo* lineage tracing and organoid models to finely map the trajectories of alveolar lineage cells during injury repair and lung regeneration. We identified how injury remodels immune system and inflammatory niches driven my macrophage dynamics orchestrate tissue regeneration during injury repair in the lungs. We also identified a distinct AT2-lineage population, Damage-Associated Transient Progenitors (DATPs), that arises during alveolar regeneration. Further, we found that chronic inflammation prevents AT1 differentiation, leading to aberrant accumulation of DATPs and impaired alveolar regeneration in chronic human lung diseases.

Importantly, while the acquisition of cellular plasticity in adult stem cells is essential for rapid regeneration after tissue injury, little is known about the underlying mechanisms governing this process. In response to severe injury in alveoli, secretory cells contribute to alveolar regeneration by giving rise to AT2 cells. However, the cellular and molecular mechanisms conferring the plasticity of secretory cells were unclear. Our study reveals the coordination of airway progenitor differentiation plasticity by inflammatory signals during alveolar regeneration. Upon damage, IL-1β signalling-dependent modulation of Jag1/2 expression in ciliated cells results in the inhibition of Notch signalling in secretory cells, which drives reprogramming and acquisition of differentiation plasticity. We identify a transcription factor Fosl2/Fra2 for secretory cell fate conversion to AT2 cells retaining the distinct genetic and epigenetic signatures of secretory lineages. We furthermore reveal that KDR/FLK-1^{+} human secretory cells display a conserved capacity to generate AT2 cells via Notch inhibition. Our results demonstrate the functional role of a IL-1β-Notch-Fosl2 axis for the fate decision of secretory cells during injury repair. Collectively, our study identified a detailed mechanism how inflammation coordinates the tissue regeneration by remodelling stem cells and their niches