Dysplastic Epithelial Repair Restricts Alveolar Regeneration after Viral Infection

Insights from integrated in vivo and organoid models

Severe respiratory viral infections, including influenza and SARS-CoV-2, frequently result in long-lasting impairment of lung function. Although acute inflammation may resolve, effective regeneration of alveolar structures often fails, predisposing patients to fibrosis and chronic respiratory symptoms. The cellular and immunological mechanisms underlying this defective repair process have remained incompletely understood.

In a recent study published in ***Cell Stem Cell***, Lu et al. report a comprehensive mechanistic investigation into how aberrant epithelial repair following viral infection actively suppresses alveolar regeneration. By combining mouse models of influenza infection with 3D epithelial–immune organoid co-culture systems, the authors demonstrate that dysplastic KRT5$^+$ basal-like cells promote the recruitment and tissue residence of effector T lymphocytes, which in turn inhibit alveolar epithelial regeneration through IFNγ–dependent mechanisms.

Dysplastic KRT5$^+$ repair cells and failed alveolar regeneration

Under physiological conditions, lung injury triggers the activation of epithelial stem/progenitor cells that replenish alveolar epithelial cells. In particular, airway club cells can differentiate into alveolar type II (AT2) cells, restoring surfactant production and gas exchange.

However, following severe viral injury, the lung often undergoes an alternative repair program dominated by KRT5$^+$ basal-like epithelial cells. While these cells rapidly restore epithelial barrier integrity, they lack alveolar differentiation potential and do not contribute to gas exchange. Lu et al. show that this dysplastic repair state is not merely due to presence in the space, but KRT5$^+$ cells' actively pathogenic processes.

The study demonstrates that KRT5$^+$ basal-like cells upregulate chemokines such as CXCL10 and CXCL11, leading to recruitment and retention of CD4$^+$ and CD8$^+$ effector T cells. These lymphocytes establish long-term residence within injured lung regions and exert a suppressive effect on epithelial regeneration.

In vivo evidence: Lung-resident T Cells actively suppress repair

Using an influenza infection model in mice, the authors observed a marked accumulation of tissue-resident CD4$^+$ and CD8$^+$ T cells in regions enriched for KRT5$^+$ basal-like cells. Spatial and temporal co-localization analyses suggested a direct interaction between these cell populations.

To assess causality, the study employed Bio X Cell's antibody, *InVivo*MAb anti-mouse CD4 or *InVivo*MAb anti-mouse CD8, to deplete of $CD4^+$ or $CD8^+$ T cells during the post-viral repair phase, deliberately initiated after viral clearance to avoid confounding effects on host defense. Depletion of either T cell subset resulted in:

- Accelerated recovery of body weight
- Improved arterial oxygen saturation
- Reduced pulmonary fibrosis
- A significant increase in AT2 cell regeneration

Lineage-tracing experiments further revealed that club cell–derived AT2 cells were markedly increased following T cell depletion, indicating that effector T cells actively suppress club-to-AT2 differentiation during the repair phase.

These findings establish lung-resident $CD4^+$ and $CD8^+$ effector T cells as functional inhibitors of alveolar regeneration rather than passive bystanders of inflammation.

Organoid co-culture models reveal direct immune–epithelial interactions

To dissect the underlying mechanisms in a controlled environment, the authors developed 3D epithelial organoid systems co-cultured with purified T cells. This approach eliminated confounding complex influences present in vivo and allowed direct interrogation of immune–epithelial interactions.

In these co-culture systems, $CD4^+$ and $CD8^+$ T cells preferentially adhered to airway-derived organoids rather than alveolar organoids. Transcriptomic analyses revealed infection-induced upregulation of CXCL10/11 and their receptor CXCR3, prompting functional testing of this chemokine axis.

Blockade of CXCR3 with *InVivo*MAb anti-mouse CXCR3 (CD183) significantly reduced T cell adhesion to airway organoids, confirming that T cell recruitment depends on CXCL10/11–CXCR3 signaling. Importantly, T cells potently suppressed alveolar organoid formation, an effect that was fully reversed by antibody (*InVivo*Mab anti-mouse IFNγ) neutralization of IFNγ but not by *InVivo*MAb anti-mouse TNFα. These data identify IFNγ as the dominant effector cytokine mediating T cell–driven suppression of alveolar regeneration.

IFNγ and chemotaxis-adhesion pathways as therapeutic targets

Having established the mechanistic framework, the authors returned to in vivo models to evaluate translational relevance. Treatment with *InVivo*Mab anti-mouse IFNγ during the repair phase improved lung function, increased $SFTPC^+$ AT2 cell numbers, and reduced

expression of chemokines associated with T cell recruitment. The magnitude of recovery closely mirrored that observed with direct T cell depletion.

In parallel, in vivo blockade of CXCR3 with *InVivo*MAb anti-mouse CXCR3 (CD183) or integrin α4β7 with *InVivo*MAb anti-mouse LPAM-1 (Integrin α4β7) reduced the number of lung-resident T cells, improved oxygenation, and attenuated fibrotic remodeling. These results demonstrate that both chemokine-mediated recruitment and integrin-dependent tissue retention are critical for sustaining the inhibitory immune niche established by dysplastic epithelial repair.

Integrated validation across in vivo and organoid systems

A notable strength of this study lies in the repeated validation of key findings across two complementary experimental platforms: mouse models of viral lung injury and three-dimensional epithelial–immune organoid cultures. This dual-model strategy enabled the authors to link physiological outcomes directly to cellular and molecular mechanisms, strengthening confidence in both causality and translational relevance.

By applying the same functional perturbations across in vivo and in vitro systems, the study provides a coherent framework explaining how aberrant epithelial repair programs reshape local immune niches and suppress regenerative capacity after viral infection.

Implications for post-viral lung disease

Collectively, the findings reported by Lu et al. redefine post-viral lung repair as an actively regulated process shaped by immune–epithelial crosstalk. Dysplastic KRT5^{+} epithelial repair cells emerge as central organizers of a suppressive immune microenvironment, recruiting and retaining effector T cells that inhibit alveolar regeneration through IFNγ signaling.

These insights have important implications for therapeutic strategies targeting post-viral lung fibrosis, prolonged respiratory dysfunction, and conditions such as long COVID. Interventions aimed at modulating IFNγ signaling, chemokine-driven recruitment, or immune cell tissue residency may offer new avenues to restore effective lung regeneration following severe viral injury.

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- *InVivo*MAb rat IgG2a isotype control, anti-trinitrophenol (BE0089)
- *InVivo*MAb rat IgG2b isotype control, anti-keyhole limpet hemocyanin (BE0090)
- *InVivo*MAb polyclonal Armenian hamster IgG (BE0091)

Reference

Lu et al. *Dysplastic epithelial repair promotes the tissue residence of lymphocytes to inhibit alveolar regeneration post viral infection*. **Cell Stem Cell** 33(1):108–124 (2026). DOI: 10.1016/j.stem.2025.12.005