PRESS RELEASE

BRIC-inStem researchers discover the dynamic nature of lung defenses

How the lung protects itself: BRIC-inStem researchers discover new mechanism

The respiratory system is our interface with the world around us. Every breath we take carries in tiny microbes, pollutants and particle matter into our lungs and airways. To protect itself the lung has an army of microscopic hair-like structures called cilia along the airway and by beating rhythmically, these cilia can sweep mucus and trapped particles out of the respiratory tract. This coordinated action of multiciliated cells forms the mucociliary escalator which is essential for respiratory health. Larger proximal airways (like the trachea) have longer cilia, while smaller distal airways (bronchioles deep in the lungs) have shorter ones. This natural gradient is suggested to optimize airflow and protection but the mechanisms directing it are unknown.

Dr. Arjun Guha's lab at BRIC-inStem works on characterizing processes that protect and repair the respiratory tract. In their latest publication in the journal Life Science Alliance, researchers from the lab have identified Notch signaling, a fundamental cell signaling pathway, as a key regulator that governs the ciliary length gradient across different regions of the airway. The study has also been highlighted on the cover page of the journal's March 2026 issue.

To investigate Notch signaling's role, the team perturbed the pathway both pharmacologically and genetically. They then analyzed ciliary length—both qualitatively and quantitatively—across different respiratory tract regions via immunofluorescence imaging and scanning electron microscopy to assess overall ciliary architecture.

"Our work shows that the ciliary length gradient is actively maintained by a single signaling pathway called Notch. When this pathway was disrupted, the gradient collapsed. Long cilia in the upper airways shortened while the typically shorter cilia in the distal airways lengthens", says Neenu Joy, the first author of the paper.

This change in the fundamental organization of the mucociliary escalator overturns a long-standing assumption in the field. It has long been held that the length gradient of cilia along the airways is hardwired during early human development and remains static. But this study reveals that this process is constantly adjusted throughout life. "The system, it turns out, is not simply damaged when perturbed—as in smokers, who exhibit globally shortened cilia—but instead has the capacity for active remodeling", says Aditya Deshpande, one of the authors of the paper.

This was further demonstrated using mice models infected with Mycobacterium tuberculosis, the bacteria that causes tuberculosis. The infection caused striking changes in the small airways. The researchers found that Notch signaling was selectively obstructed in the deepest small airways causing the cilia there to grow significantly longer. This suggests that the mucociliary escalator retunes itself to repair the most affected parts.

The discovery underscores the growing recognition that small airway biology is central to respiratory disease. Infections, inflammation and other illnesses of the lung are known to begin or progress in the small distal airways. Previous studies have reported abnormal cilia lengths in conditions such as smoking-related lung disease, asthma, chronic obstructive pulmonary disease *etc*.

“The implications of our report are particularly resonant in the Indian context, where tuberculosis and chronic respiratory disease remain major public-health challenges. By revealing that airway defenses are structurally adaptable, this work adds a new layer to how we think about resilience and vulnerability in the lung”, explains Neenu.

Beyond its societal implications, the findings open doors to new scientific questions. By showing that airway defense is actively regulated by cellular signaling, these results invite further exploration into how such alterations shape lung and disease biology. “The central insight is both modest and profound: the lung does not merely defend itself—it adjusts how it defends itself. Even in one of biology’s most familiar systems, there is still room for surprise”, remarks Dr. Arjun Guha, principal investigator at BRIC-inStem who led the study.

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