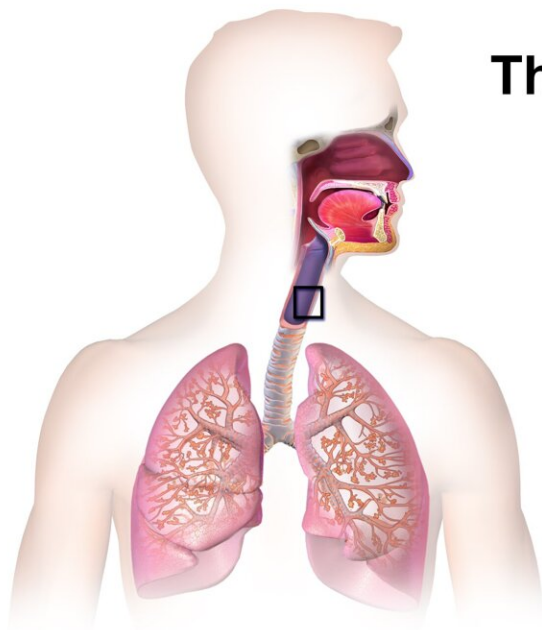


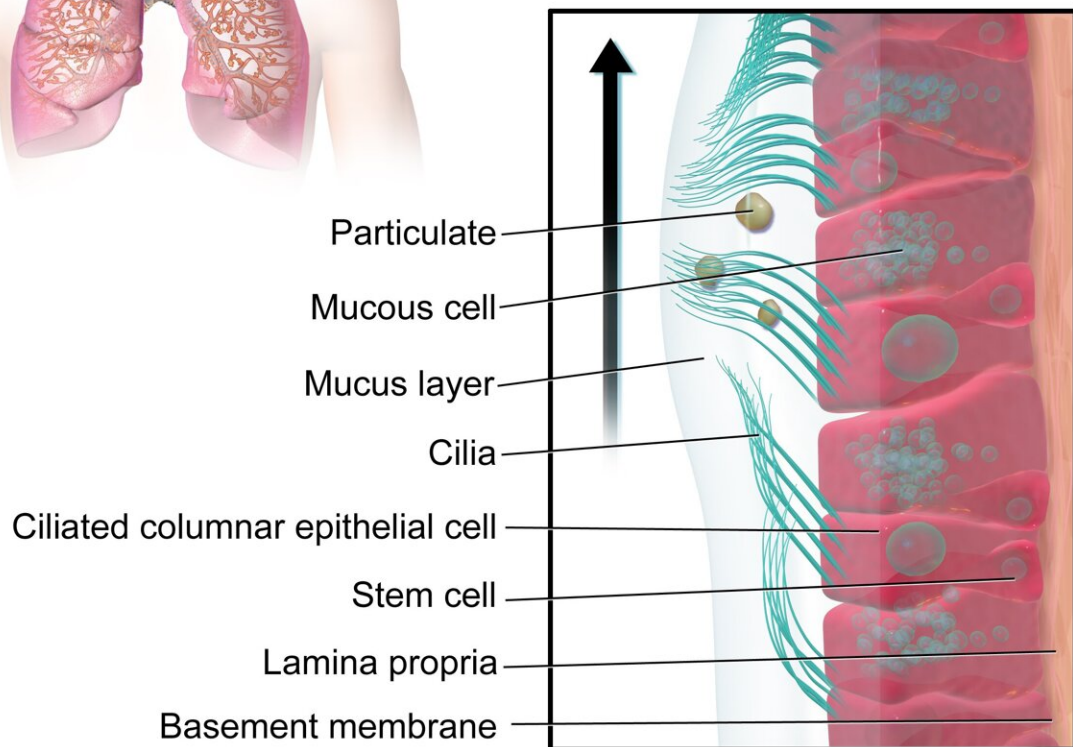
Newly identified embryonic airway cell type holds promise for respiratory disease therapies

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The Respiratory Epithelium

Movement of mucus to the pharynx



The respiratory epithelium. Credit: Bruce Blaus. Blausen.com staff (2014). Credit: Medical gallery of Blausen Medical 2014, WikiJournal of Medicine

An international research team has discovered a new cell state in embryonic airway development that has been overlooked until now. It could pave the way for new approaches to treating chronic respiratory diseases and holds promise for new airway biology therapies.

During specialization, the [individual cells](#) form different airway [cell types](#), a process that can include a period of uncertainty, although they are seemingly coded to develop specific airway cells. This uncertainty helps cells to specialize but also respond to an ever-changing environment.

These are the findings presented by an international team of researchers led by Kedar Natarajan, Associate Professor at DTU, and published in *Science Advances*.

"This discovery may have the potential to be good news for patients with dysregulated airway cell types, including in asthma, COPD, and cystic fibrosis," says Kedar Natarajan.

Human beings consist of trillions of cells composed of several cell types performing specialized roles within organs. How the cell types, particularly specialized cells in the airways, are formed during the early phase of embryo formation (embryonic development) is of interest for [chronic diseases](#) and therapy.

Researchers have used new state-of-art sensitive technologies as well as

sequencing and computational methods to understand the process of how these cell types are formed during the early phase of embryo formation, and they have found evidence of a non-standard model, wherein cells in a continuous non-hierarchical manner undertake decisions, unlike in other well-studied systems.

"Our time-course analysis of [embryonic development](#) captures a new progenitor, i.e., parent cell population in the mucociliary epithelium, such as the airway, composed of different cell types like basal cells, ionocytes, and goblet cells. This progenitor population occurs much earlier than expected and contributes to the formation of all major cell types, highlighting the crucial role of cellular heterogeneity before committing to a specialization. This means that the decision for some cell types is made long before we can see it," says Kedar Natarajan.

Chronic respiratory diseases are a major killer worldwide

The researchers have studied a specific type of progenitor cell from tissue in the [respiratory tract](#), the so-called mucociliary epithelium. The molecular mechanisms enabling cells to specialize over time during mucociliary epithelial development have been relatively less explored until now.

The different cell types provide natural immunity and remove pathogens, dust, and other particles from the airway tract while maintaining optimal osmotic, ionic, and acid-base levels. The formation and function of the specialized cells are affected in people who suffer from respiratory diseases such as asthma and COPD. These chronic diseases can be alleviated today, but there is still no cure.

According to the World Health Organization (WHO), respiratory

problems are responsible for about 15% of all deaths. These include diseases such as asthma and COPD, but also cancer, pneumonia, and cystic fibrosis. [WHO estimates](#) that 339 million people worldwide are affected by asthma alone.

"To understand what happens when [chronic respiratory diseases](#) occur, we need to have a better picture of all the states the cell goes through, especially during the early stages of cell type formation. We often study what happens to a cell after it has gone bad and then try to repair it. We should also study how the cell is formed to better understand how it is broken. The body's cells renew themselves all the time, so when we know how the cell's decision can be influenced along the way, that knowledge can help open a new door to how we treat diseases like asthma or COPD," explains Kedar Natarajan.

"Our work provides an insight into the changes in the state of the cells that occur when the mucociliary tissue develops. It helps to dissect the mechanisms involved during the formation of the tissue. And this knowledge can be useful in developing regenerative treatments for chronic lung diseases, for example," he says.

A sensible system keeps the lungs clean

The tissue of the respiratory tract consists of a complex system of cells with several fixed functions. The system is collectively called the mucociliary epithelium. Mucus means slime and is the Latin name for the mucus that covers and protects the mucous membrane. Cilia are the tiny hairs that line the mucous membrane, and the epithelium is the term for cells covering the body's internal and external surfaces.

The different mucociliary cells perform four central functions, which together enable the function and protection of the airways. The mucus-producing cells form a defensive barrier against pathogens, dirt, and

bacteria, while the ciliated cells interact with liquids and drive flow and clearance of trapped particles via coordinated beating. The ion-regulating cells are needed to maintain osmotic, ionic, and acid-base levels, while basal cells can replenish required cell types toward normal function upon damage.

All originate from the same cell type, predestined to develop into the cells that make up the mucociliary epithelium. During the development process, the cell undergoes distinct phases (gastrula, neurula, early and late-tailbud stages) to form all major cell types. However, the neurula stages and respective cell divisions define how cells turn into the four specialized mucociliary epithelial cell types over time.

Why can it go wrong along the way?

Together, the cells ensure that you can breathe without the airways being blocked or damaged by, e.g., the dust in the air you inhale. In [respiratory diseases](#), the cells are derailed in their development and continue to develop from that new point.

"We need to understand what happens in the individual cell at different stages of the tissue's development—i.e., are there discrete stages where differentiation takes place, or is it random? If we understand how cells undertake these fate decisions, we may, among other things, be able to fix the errors in functions that could develop along the way," says Kedar Natarajan.

Defects in cell type functions lead to disease phenotypes typical in people who suffer from, e.g., asthma, COPD, and cystic fibrosis. This makes the airways more susceptible to infections and diseases and can weaken the function of the lungs.

"More than 20 different diseases in the respiratory tract are caused by

the cilia on the surface of the mucosal tissue being damaged—they might, for example, be too small or move uncoordinatedly. This means that they cannot sweep properly so that the dust can be directed away from the airways," says Kedar Natarajan.

Cell transformations have been studied in frogs

The researchers have taken the mucociliary cells of the *Xenopus* frog as their starting point. The development in the frog's cells is similar to that of the mucociliary cells in humans. The difference is that it is easier to distinguish the four directions in which the cells develop in the pluripotent cells.

The researchers have mapped the development of each cell at ten different developmental stages, starting from undifferentiated cells (stage 8) all the way to differentiated cells (stage 27), where major cell types are formed for specific functions. Interpreting how cells differentiate across all stages is like understanding a highly elaborate family tree, analyzing what differs from generation to generation.

In total, the researchers studied approximately 35,000 cells. The researchers have contented themselves with studying the changes that occur between the stages and have therefore carefully evaluated approx. 3,000 genes for each cell. This resulted in enormous amounts of data that made the researchers aware that some of the cells go through a previously unknown state (termed "early epithelial progenitors") and undergo specialization in a distinct manner.

"During our work, we discovered a progenitor population that we believe was previously missed. We call the cells the early epithelial progenitors. They undertake specialization to form late-stage ionocytes, goblet cell, and basal cell populations. Therefore, we propose a model wherein early epithelial progenitors undergo fate transitions in a continuous non-

hierarchical manner that is distinct from the standard model," says Kedar Natarajan.

The mucociliary cells perform four central functions, which together enable the function and protection of the airways. The [mucus](#)-producing goblet cells form a defensive barrier against pathogens, dirt, and bacteria. The multiciliated cells interact with liquids, driving flow and clearance of trapped particles via coordinated beating. The ionocytes regulate osmotic, ionic, and acid-base levels, while basal cells can replenish required cell types toward normal function upon damage.

More information: Julie Lee et al, A single-cell, time-resolved profiling of *Xenopus* mucociliary epithelium reveals nonhierarchical model of development, *Science Advances* (2023). [DOI: 10.1126/sciadv.add5745](#)

Provided by Technical University of Denmark

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