Sleuths follow lung stem cells for generations to shed light on healing

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More than one kind of stem cell is required to support the upkeep and repair of the lungs, according to a new study published in the journal *Cell Stem Cell*.

Scientists at Duke University Medical Center painstakingly followed and counted genetically labeled cells in the mouse lung for over a year, under differing conditions, to learn more about natural renewal and healing processes. This information may shed light on what goes wrong in conditions like lung cancer, chronic bronchitis and asthma.

"We are learning the exact processes that maintain the various regions of the lung in tip-top condition and what happens when things go wrong," said Brigid Hogan, Ph.D., chair of the Duke Department of Cell Biology and senior author of the study. "Normally, the lung is beautifully organized, with the exact proportion of secretory and ciliated cells lined up next to each other to get their jobs done." The secretory cells lubricate and protect, while the hair-like projections of the ciliated cells waft the secretions up and out of the lungs.

In humans, under conditions of heavy smoking, or infection or inflammation due to asthma or cystic fibrosis, repeated cycles of damage and repair lead to a messy arrangement, she said. "You can get patches of cells building up in a stacked, flattened formation like skin cells. Some cells multiply too fast; others may make too much mucus."

The team tagged secretory cells, called Clara cells, found in both the trachea and bronchioles, the airway branches inside the lung. They followed them in normal mice and during the amazingly efficient repairs after damage by too much oxygen or other environmental stresses.

They tested the theory that there are BASCs (bronchioalveolar stem cells). These purportedly are on the border between the bronchioles and alveoli, which are the small air sacs where gas exchange takes place. BASCs were thought to replenish both regions of the lung.

Instead, the cells they labeled and followed in the bronchioles only renewed the airways and not the alveoli; they found no evidence for a special BASC population.

The Duke team was also surprised to find that the proportion of tagged Clara cells in the airways stayed the same for over a year. What's more, the genetic tag slowly appeared in ciliated cells, which told them that the secretory cells both make more of themselves and give rise to ciliated cells - a switch that had been suspected but never shown directly. Since the tagged cells renew over a long time and give rise to ciliated cells, they behave like long-term stem cells even though they are differentiated.

When the scientists tagged secretory cells in the trachea and followed them for a year, they found that the labeled cells gradually were lost. They could multiply and make ciliated cells but didn't do this for long. As the tagged cells were lost by wear and tear they were replaced by the descendants of unlabeled cells. From other experiments, Hogan and her colleagues think these replenishing cells are basal cells.

"In the wider trachea, there is a population of basal cells that are more like classical stem cells in being undifferentiated," Hogan said. Cells like these basal stem cells are found in the airways and bronchioles of human lungs. "It is important to know what these stem cells are doing in the human lung," Hogan said.

Until now, the lineage labeling tools had not been available for lung Clara cells. Postdoctoral fellow Emma Rawlins' efforts to tag the cells and count the daughters for over a year were "heroic," Hogan said.

"You really need this particular genetic flag to know exactly what a cell's fate is," Hogan said. "If you just stain the cells, this tells you only what they look like. It doesn't say who the parents are, and who begets whom, if you will. You have to count and work out the family tree."

Many questions remain. "While we know secretory cells can give rise to ciliated cells, we don't know what controls this switch so that the correct proportion is always made," Hogan said. "In the airways of people with asthma there are many goblet cells that make mucus, but we don't know where these cells come from. We also need to search for the specialized stem cell that gives rise to alveolar cells."

Source: Duke University Medical Center (news : web)

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