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Scientists create airway spheres to study lung diseases

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Using both animal and human cells, Duke University Medical Center scientists have demonstrated that a single lung cell can become one of two very different types of airway cells, which could lead to a better understanding of lung diseases.

From this single "basal" cell, a small, squat stem cell that divides to replenish the lung lining layer, scientists created 3-D hollow spheres that were lined inside with both ciliary and secretory cells. This 3-D model can be used to study dynamic processes underlying lung diseases, including cancer, said Brigid Hogan, Ph.D., chair of the Duke Department of Cell Biology and senior researcher of the study, which was published in *PNAS Early Edition*.

"Now that we have this 3-D model and information about the gene expression 'signature' of basal cells, we are in a strong position to see what happens when lung-cell behavior goes awry," Hogan said. "We might, for example, be able to activate an oncogene (a cancer-causing gene) or other factors to see how lung cancer might develop in the airways. Amazingly, almost nothing is known about lung basal cells, which are so important to health and make up nearly a third of the cells in the human airways."

Normally, basal stem cells maintain the airways by turning over slowly into new ciliated cells and secretory cells. Ciliated cells resemble waving brooms that sweep along particles and distribute secretions that are needed in the airways, and secretory cells provide the antibacterial and

lubricating secretions. These two types of cells are neatly arranged in equal proportions in healthy lung airways. However, when lungs are affected by maladies like cancer, chemical damage, cystic fibrosis or asthma, the balance of these cells can be thrown off.

By learning the role these basal cells play in maintaining the airway tissue, the scientists were able to create an entirely new way to study them.

"We put a lot of effort into developing this model, so that we and other groups can test the ability of individual airway progenitor cells to divide and differentiate under defined conditions," said lead author Jason Rock, Ph.D., a postdoctoral associate in the Duke Department of Cell Biology. "Now we can change the culture conditions to investigate mechanisms that underlie pathological conditions, including chronic asthma and cancer."

The work was a collaboration of cell biologists, Mark Onaitis, M.D., of the Department of Surgery at Duke University Medical Center, and Scott H. Randell, PhD., of the Cystic Fibrosis/Pulmonary Research and Treatment Center at the University of North Carolina in Chapel Hill.

The scientists isolated basal cells, set each separately in a gel suspension, and observed the cells growing into a hollow sphere as they divided. Analysis shows that the basal cells remain on the outside of the sphere, while inside the hollow was lined in an equal arrangement of cilial and secretory cells, as in nature.

"This basal cell is making daughters, which are polarized and retain their orientation so that they will form a structure with luminal (airway lining) cells on the inside," Hogan said. "Only about 5 percent of the basal cells we isolated and put into gel formed these spheres; perhaps these are the ones that are normally ready to leap into action when they are

challenged."

After painstakingly sorting individual green fluorescent mouse basal cells from the other lung tissue cells, the scientists studied the genes expressed in these mouse cells using microarray technology. They found more than 600 genes preferentially expressed in the basal cells compared with the other cells.

"We found that many of these genes are similar to genes expressed in stem cells in other tissues," Hogan said. "We think these genes are helping these cells to stay 'quiet' and keep them from dividing until they get the right signal."

The researchers also found that one gene expressed in the basal cells encodes a surface receptor, also found on human lung basal cells. "This meant we were able to use a labeled antibody against this receptor to efficiently extract human lung basal cells to create the human bronchospheres for study," Hogan said.

Source: Duke University Medical Center (news : web)