

SOX17 as a Target for the Treatment and Diagnosis of Lung Damage

TECHNICAL FIELD

Therapeutic, Diagnostic: Lung Damage (2004-1102)

BACKGROUND

The respiratory tract consists of an extensive epithelial cell surface that is in constant contact with gases, particles, and pathogens from the outside environment. The lung needs to respond rapidly to damage from outside agents by repairing the epithelial surfaces involved in gas exchange, host defense and surfactant homeostasis. The pathways governing lung repair after damage are not well understood, but result in the rapid proliferation and differentiation of diverse cell types to preserve lung function.

The SOX17 gene is a key regulator mediating lung repair processes, and therefore presents a novel target for the diagnosis and treatment of lung damage.



TECHNOLOGY

In a mouse model of lung injury, Dr. Whitsett's team demonstrated that ciliated, bronchiolar epithelial cells underwent a rapid squamous transdifferentiation after lung damage. These dedifferentiated cells proliferated and then redifferentiated into ciliated and non-ciliated cell types of the respiratory epithelium. The SOX17 protein, a member of the High Mobility Group family of DNA binding proteins, was a key regulator governing the regeneration of the bronchiolar epithelium after lung damage. In transgenic mice, expression of SOX17 in the lung was sufficient to induce ciliated and progenitor cell behavior in the fetal and adult lung. SOX17 also activated the mouse FOXj1 promoter in an in vitro Hela cell reporter gene assay. Expression of β -catenin and Stat-3 coincided with SOX17 expression and preceded the expression of transcription factors critical to lung epithelial cell differentiation including TTF-1, FOXa2 and FOXj1. A transcriptional program similar to that involved in normal lung morphogenesis coordinated squamous metaplasia and redifferentiation of progenitor cells following lung injury. Furthermore, this work has identified bronchiolar epithelial cells, previously thought to be terminally differentiated, as a source of progenitor cells that mediate lung repair.

The invention describes novel methods for regulating SOX17 to activate airway epithelial progenitor cell behavior for purposes of prophylaxis and/or treatment of lung damage. The invention also describes methods for detection of SOX17 protein or mRNA as a diagnostic for pulmonary status.

APPLICATIONS

1. Target for development of treatment for lung damage
2. Diagnostic indicator of lung damage

ADVANTAGES

Potential to develop new therapeutic and diagnostic markets

INVESTIGATOR

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STATUS

Patent applications pending.

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SOX17 as a Target for the Treatment and Diagnosis of Lung Damage

THE INVENTOR

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BACKGROUND

Jeffrey A. Whitsett, MD, is chief of the Section of Neonatology, Perinatal and Pulmonary Biology at Cincinnati Children's Hospital Medical Center.

Dr. Whitsett received his medical degree from Columbia University, in New York, and has been a faculty member since 1977. He is internationally known for his research in pulmonary medicine, as well as for his clinical expertise in neonatology.



Dr. Whitsett has made a series of groundbreaking contributions in pulmonary medicine. His major pioneering work has been on surfactant proteins A, B, C, and D, cloning their genes, and clarifying their roles in lung development.

Throughout his career, Dr. Whitsett has had the remarkable ability to move from molecular biology, to animal models, to diagnosis and therapy of human disease. He played a critical role in making surfactant protein replacement a routine tool for treating immature lungs and respiratory distress syndrome in premature infants. His laboratory has contributed to the identification of a number of genes critical for lung formation and function. Mutations in genes regulating surfactant homeostasis were shown to cause acute and chronic lung disease in infants and adults.

Dr. Whitsett is a member of the Institute of Medicine, National Academy of Sciences and is the recipient of the Mead Johnson Award, a National Institutes of Health (NIH) Merit Award, the first Julius Comroe Lectureship in Pulmonary Research from FASEB, the William Cooper Procter Award from Cincinnati Children's, the Amberson Lecture Award of the American Thoracic Society, and the prestigious Daniel Drake Medal for scientific contributions from the University of Cincinnati College of Medicine.

Dr. Whitsett is the author of over 400 papers in both the basic science and clinical literature.