Land of hope and dreams

Selection of life science and translational medicine literature

by Marco Confalonieri

MicroRNAs (miRNAs) are a class of 19-22 nucleotides non-coding small RNAs that control the expression of a large number of genes by binding to the 3'UTR of targets and blocking translation or by causing degradation of target mRNA.

MicroRNAs have emerged as an important class of small RNAs encoded in the genome, acting as master regulators of gene expression at post-trascriptional level. Recent studies have indicated that microRNAs appear to be associated with many disease processes. Because they are thought to be single molecular entities that dictate the expression of fundamental regulatory pathways, microRNAs represent potential drug targets for controlling many biologic and disease processes.

Yale University researchers are studying a potential new treatment that reverses the effects of pulmonary fibrosis, a respiratory disease in which scars develop in the lungs and severely hamper breathing.

The treatment uses a microRNA mimic, miR-29, which is delivered to lung tissue intravenously. In mouse models, miR-29 not only blocked pulmonary fibrosis, it reversed fibrosis after several days.

The microRNA-29 family is a well-established regulator of extracellular matrix genes. Accumulating studies have demonstrated that miR-29 family participates in the development of liver fibrosis, renal fibrosis, pulmonary fibrosis, cardiac fibrosis. It was also known the comprehensive role of miR-29 family in moderating profibrotic effect and its potential as therapeutic approach to fibrosis diseases. The expression of the three miR-29 family members is consistently down-regulated in a number of pathological fibrotic conditions, including cardiac, renal, hepatic, and pulmonary fibrosis, as well as systemic sclerosis. Numerous studies in cell-culture and genetic replacement in rodents have also demonstrated the potential of miR-29 normalization to correct many drivers of pathological fibrosis. The Yale University study is the first one showing the potential therapeutic of miR-29 *in vivo*. The findings were recently published in the journal EMBO Molecular Medicine.

Another group of researchers from the People's Republic of China found that another microRNA type, the 26a family, is fundamentally down-regulated during pulmonary fibrosis. Over-expression of microRNA-26a is able to contrast the experimental pulmonary fibrosis induced by bleomycin inhibiting the nuclear translocation of p-Smad3 through directly targeting Smad4, which determines the nuclear translocation of p-Smad2/Smad3. So, also microRNA-26a could be a new promising molecular treatment to reverse pulmonary fibrosis.

1) MicroRNA mimicry blocks pulmonary fibrosis

Montgomery RL, Yu G, Latimer PA, et al.
Embo Mol Med 2014;6:1347-56

Abstract

Over the last decade, great enthusiasm has evolved for microRNA (miRNA) therapeutics. Part of the excitement stems from the fact that a miRNA often regulates numerous related mRNAs. As such, modulation of a single miRNA allows for parallel regulation of multiple genes involved in a particular disease. While many studies have shown therapeutic efficacy using miRNA inhibitors, efforts to restore or increase the function of a miRNA have been lagging behind. The miR-29 family has gained a lot of attention for its clear function in tissue fibrosis. This fibroblast-enriched miRNA family is downregulated in fibrotic diseases which induces a coordinate increase of many extracellular matrix genes. Here, we show that intravenous injection of synthetic RNA duplexes can increase miR-29 levels in vivo for several days. Moreover, therapeutic delivery of these miR-29 mimics during bleomycin-induced pulmonary fibrosis restores endogenous miR-29 function whereby decreasing collagen expression and blocking and reversing pulmonary fibrosis. Our data support the feasibility of using miRNA mimics to therapeutically increase miRNAs and indicate miR-29 to be a potent therapeutic miRNA for treating pulmonary fibrosis.

2) The antifibrotic effects and mechanisms of microRNA-26a action in idiopathic pulmonary fibrosis

Liang H, Xu C, Pan Z, et al.
Mol Ther 2014;22:1122-33

Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and high-lethality fibrotic lung disease characterized by excessive fibroblast proliferation, extracellular matrix accumulation, and, ultimately, loss of lung function. Although dysregulation of some microRNAs (miRs) has been shown to play important roles in the pathophysiological processes of IPF, the role of

miRs in fibrotic lung diseases is not well understood. In this study, we found downregulation of miR-26a in the lungs of mice with experimental pulmonary fibrosis and in IPF, which resulted in posttranscriptional derepression of connective tissue growth factor (CTGF), and induced collagen production. More importantly, inhibition of miR-26a in the lungs caused pulmonary fibrosis in vivo, whereas overexpression of miR-26a repressed transforming growth factor (TGF)-β1-induced fibrogenesis in MRC-5 cells and attenuated experimental pulmonary fibrosis in mice. Our study showed that miR-26a was downregulated by TGF-β1-mediated phosphorylation of Smad3. Moreover, miR-26a inhibited the nuclear translocation of p-Smad3 through directly targeting Smad4, which determines the nuclear translocation of p-Smad2/Smad3. Taken together, our experiments demonstrated the antifibrotic effects of miR-26a in fibrotic lung diseases and suggested a new strategy for the prevention and treatment of IPF using miR-26a. The current study also uncovered a novel positive feedback loop between miR-26a and p-Smad3, which is involved in pulmonary fibrosis.