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COMMENTARY

Micro RNAs: The Future of Idiopathic Pulmonary Fibrosis Therapy

Tara Vinyette Saco · Prasanna Tamarapu Parthasarathy · Young Cho · Richard Lockey · Narasaiah Kolliputi

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Idiopathic pulmonary fibrosis (IPF) is a debilitating, chronically progressive lung disease that leads to significant morbidity and mortality [1]. Although it is a fairly uncommon disease, its incidence has been increasing over the past decade [2]. One of the key elements contributing to the development of IPF is the inability to halt the progression of damage to lung epithelial cells. The pathogenic mechanisms involved in this process include excessive inflammation, overactivity and hyperproliferation of fibroblasts, and inadequate repair of epithelial cell injury [3]. Currently, no treatment modality has been proven to be effective in preventing or reversing the parenchymal damage occurring in IPF. However, a surge in the amount of research pursuing future therapies has occurred in recent years. A field of study that appears to be particularly promising in the development of new IPF treatments is the study of epigenetic regulatory mechanisms involved in the pathogenesis of IPF. Fig. 1

Epigenetic factors involved in the pathogenesis of IPF, including micro RNAs (miRNAs), may be the key to the development of future treatments for this disease [4]. miRNA expression can be controlled by the very epigenetic mechanisms they themselves regulate, including DNA methylation and histone modification. Thus, the number of ways they can be utilized in the development of targeted therapies for many diseases, including IPF, seems limitless [5].

Dakhlallah et al. recently demonstrated the role of epigenetic mechanisms in IPF [3]. These researchers investigated the role of miRNA-17–92 cluster (miR-17–92) in the development of IPF, which is presumed to inhibit specific pro-fibrotic genes, including transforming growth factor-β (TGF-β), metalloproteinases, and type 1 α1 collagen (COL1A1) [3]. This cluster is also involved with lung development, as evidenced by animal studies demonstrating death by asphyxiation in mice lacking the miR-17–92 cluster [6], and high proliferation rates of undifferentiated lung epithelial cells in mice overexpressing this cluster [7]. Expression of miR-17–92 is silenced by hypomethylation via DNA (cytosine-5)-methyltransferase 1 (DNMT-1), the DNMT that is most closely involved with cellular and tissue repair.

Dakhlallah et al. demonstrated that lung fibroblasts and epithelial cells from IPF patients had increased DNMT-1 expression, leading to hypermethylation of and subsequently decreased levels of miR-17–92 expression [3]. This leads to upregulation of pro-fibrotic genes, especially TGF-β, which has been shown to lead to the overproduction of miRNA-21 (miR21), an miRNA that silences inhibitors of TGF-β expression, leading to a vicious cycle of unchecked fibrosis in IPF [8]. This is further supported by the fact that decreased miR-21 expression inhibits the pro-fibrotic effects of bleomycin in the lung parenchyma of mice [8]. In the study by Dakhlallah et al., administration of the chemotherapeutic demethylating agent, 5′-aza-2′-doxyctidine, in the IPF patients leads to upregulation of miR17–92, with a subsequent decrease in DNMT-1 levels and downregulation of genes involved in fibrosis. It can be eluded from

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T. V. Saco · P. T. Parthasarathy · Y. Cho · R. Lockey · N. Kolliputi (✉)
Division of Allergy and Immunology, Department of Internal Medicine, Morsani College of Medicine, University of South Florida, 12901 Bruce B. Downs Blvd., MDC 19, Tampa, FL 33612, USA
e-mail: nkollipu@health.usf.edu

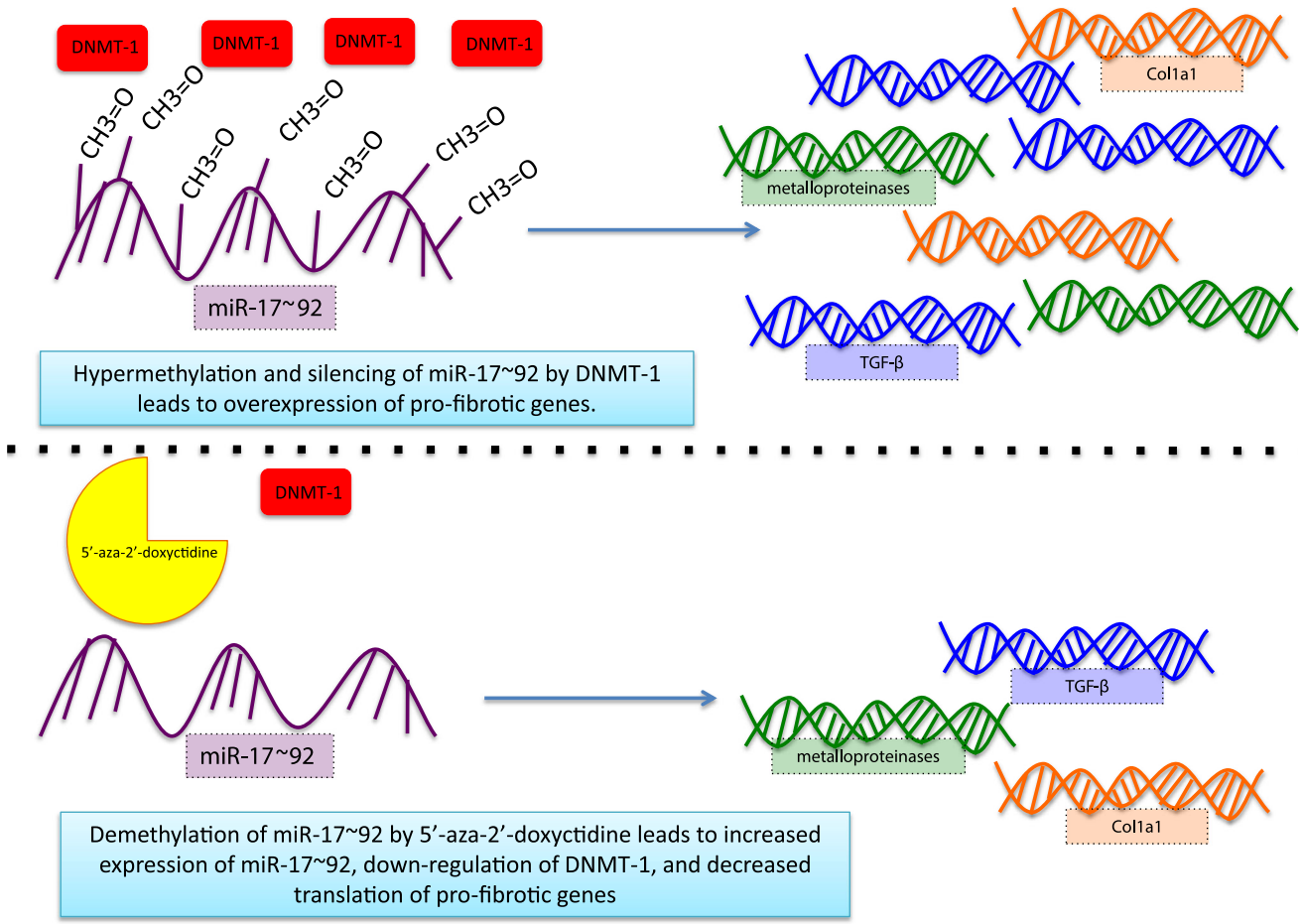

Fig. 1 Summary of miR-17–92 regulation in idiopathic pulmonary fibrosis

these findings that the miR-17–92 cluster is vital to lung parenchymal repair in IPF [3].

This same mechanism was also seen in mice with pulmonary fibrosis induced by bleomycin. Dakhlallah et al. then went one step further by administering 5′-aza-2′-doxyctidine to see if subsequent upregulation of miR17–92 would lead to reversal of the pulmonary fibrosis in these mice. The mice treated with 5′-aza-2′-doxyctidine did not experience significant reversal of their pulmonary fibrosis because the 5′-aza-2′-doxyctidine did not lead to breakdown of collagen already present in the lung parenchyma. However, 5′-aza-2′-doxyctidine administration did prevent further production of collagen in the mice's lungs, and thus slowed the progression of their IPF. These results are analogous to those obtained in a study conducted by Bechtel et al. revealing that 5′-aza-2′-doxyctidine decreased DNMT-1 methylation of *RASAL1*, an inhibitor of *Ras* expression, leading to slowed progression of renal fibrosis. Interestingly, other studies have shown that *RASAL1* expression is not only controlled via DNMT-1, but also through TGF-β and many miRNAs that make up the miR17–92 cluster [9].

The study by Dakhlallah et al. presents some compelling results that support conducting further human studies examining the efficaciousness of 5′-aza-2′-doxyctidine in IPF patients [3]. A side effect of the drug that could possibly limit its effectiveness is its tendency to lead to myelosuppression with subsequent pancytopenia. It can also be concluded from this study that direct DNMT-1 inhibitors may provide an alternative IPF therapy. Animal and human studies should be conducted to investigate the effectiveness of direct DNMT-1 inhibitors in the prevention of progression and possible reversal of IPF. Human trials examining the effect of exogenous administration of miR-17–92 on the progression of IPF pathology should also be pursued. In all, epigenetic therapies represent a versatile and promising new avenue for IPF treatment. Future studies should examine these possible therapies as they provide an arsenal of new weapons to be used in the battle against IPF.

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References

1. Olson, A. L., & Swigris, J. J. (2012). Idiopathic pulmonary fibrosis: diagnosis and epidemiology. *Clinics in Chest Medicine, 33*(1), 41–50.
2. Ley, B., Collard, H. R., & King, T. E, Jr. (2011). Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine, 183*(4), 431–440.
3. Dakhlallah, D., et al. (2013). Epigenetic regulation of miR-17–92 contributes to the pathogenesis of pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine, 187*(4), 397–405.
4. Nuovo, G. J., et al. (2009). A methodology for the combined in situ analyses of the precursor and mature forms of microRNAs and correlation with their putative targets. *Nature Protocols, 4*(1), 107–115.
5. Cho, J. H., et al. (2011). Systems biology of interstitial lung diseases: integration of mRNA and microRNA expression changes. *BMC Medical Genomics, 4*, 8.
6. Ventura, A., et al. (2008). Targeted deletion reveals essential and overlapping functions of the miR-17 through 92 family of miRNA clusters. *Cell, 132*(5), 875–886.
7. Lu, Y., et al. (2007). Transgenic over-expression of the microRNA miR-17-92 cluster promotes proliferation and inhibits differentiation of lung epithelial progenitor cells. *Development Biology, 310*(2), 442–453.
8. Liu, G., et al. (2010). miR-21 mediates fibrogenic activation of pulmonary fibroblasts and lung fibrosis. *Journal of Experimental Medicine, 207*(8), 1589–1597.
9. Bechtel, W., et al. (2010). Methylation determines fibroblast activation and fibrogenesis in the kidney. *Nature Medicine, 16*(5), 544–550.