

BSTR BRIGHT LIGHTS REVIEW

December 2015

PUBLISHED ARTICLE

[MicroRNA-144 dysregulates the transforming growth factor- \$\beta\$ signaling cascade and contributes to the development of bronchiolitis obliterans syndrome after human lung transplantation.](#)

Xu Z, Ramachandran S, Guasekaran M, et al. J Heart Lung Transpl 2015;34:1154-62.

REVIEW TITLE

Bronchiolitis obliterans syndrome after lung transplantation: what has basic science done for this lately?

REVIEW AUTHORS

John J. Squiers, B.S.E.¹; Brian Lima, M.D.²; J. Michael DiMaio, M.D.^{1,2}

AFFILIATIONS

¹Baylor Research Institute
Baylor Scott & White Health
Dallas, TX

²Department of Cardiac and Thoracic Surgery
Baylor University Medical Center
Baylor Healthcare System
Dallas, TX

CORRESPONDING AUTHOR

J. Michael DiMaio
Baylor Research Institute
3310 Live Oak, Suite 501
Dallas, TX 75204
Email: jmdimaio@yahoo.com

DISCLOSURE

The authors have no conflicts of interest to report.

WORD COUNT: 940

EDITORIAL

Bronchiolitis obliterans syndrome (BOS) is a major limitation of long-term allograft survival, and up to 75% of patients undergoing lung transplantation develop BOS after 10 years.¹ BOS is the result of an inflammatory process that ultimately causes partial or complete fibrotic occlusion of the small airways.² However, our current understanding of the molecular signaling pathways implicated in the inflammation and fibrosis associated with BOS is limited. In the September issue of *The Journal of Heart and Lung Transplantation*, Xu and colleagues from the Washington School of Medicine in St. Louis reported the results of their excellent investigation entitled “[MicroRNA-144 dysregulates the transforming growth factor- \$\beta\$ signaling cascade and contributes to the development of bronchiolitis obliterans syndrome after human lung transplantation.](#)”³ We wish to highlight the work of these authors in a new initiative of the Scientific Council on Basic Science & Translational Research, “BSTR Bright Lights,” in the hopes of demonstrating the significance of their work in a context that is immediately relevant to practicing clinicians.

The investigation conducted by Xu and colleagues was apparently motivated by two key findings previously reported in the literature. First, it has been established that increased expression of transforming growth factor- β (TGF- β) can be found in biopsy samples of the lungs of BOS+ patients,⁴ and TGF- β is known to play a key role in the pathogenesis of lung fibrosis by upregulating the activity of cells responsible for fibrogenesis.⁵ Second, the dysregulation of microRNA-144 (miR144) was recently implicated in bleomycin-induced pulmonary fibrosis in mice.⁶ Therefore, Xu and colleagues sought to investigate the potential roles of TGF- β and miRNA144 in the pathogenesis of BOS, as well as a potential relationship in molecular signaling between these two molecules.

Through a series of elegantly designed experiments, the authors were able to demonstrate several remarkable findings. Most notably, expression of miR144 was significantly higher in lung biopsy specimens of human BOS+ patients as compared to BOS- patients. This increased expression of miR144 was shown to upregulate the TGF- β signaling cascade that results in the fibrogenic processes leading to BOS. The authors also transfected miR144 into cultured lung fibroblast cells to show that this molecule induced expression of several important markers of fibrosis. Taken together, these results suggest that the attenuation of miR144 expression may be able to prevent the development of BOS in patients undergoing lung transplantation.

The work of Xu and colleagues is worth highlighting because their research begins to outline a new therapeutic approach to managing lung transplant recipients. Specifically, by demonstrating the involvement of miR144 on the development of BOS, the authors have moved the field one step closer to a *molecular-level* therapeutic approach. MicroRNA (miRNA) molecules are ubiquitous throughout biological processes. Their role in disease as well as in potential therapies continues to be delineated in virtually every field of medicine.⁷ First discovered two decades ago,⁸ miRNAs are key players in the post-transcriptional regulation of gene expression.⁹ These molecules reduce gene expression by base-pairing with conjugate regions on messenger-RNA (mRNA) molecules to promote cleavage, destabilization, or ineffective translation of the mRNA.¹⁰ With the knowledge that miR144 is implicated in the development of BOS, this molecule may eventually serve as a target of a molecular therapeutic agent that could be offered to lung transplant recipients to extend the survival of their lung allograft by hindering the pathological process that results in BOS.

Before scientists and clinicians can begin to target miR144 in this manner, however, further work is certainly necessary. It is important to note that the individual pathways on which individual

miRNA molecules can act are often innumerable, and therefore the downstream effects of targeted manipulation of miRNA molecules may have unforeseen consequences.¹¹ Blindly targeting miR144 to prevent BOS could cause harmful side effects or even result in the opposite effect of that intended. Further research is therefore necessary to delineate which additional pathways are regulated by miR144 and what effects the attenuation of miR144 may have on these pathways. Nevertheless, we commend Xu and colleagues for their recently published manuscript. Although the work conducted by these scientists and physicians was completed at the bench-top, their findings can—and should—be translated into clinically-relevant therapies for lung transplant patients in the coming years.

REFERENCES

- ¹ Christie JD, Edwards LB, Aurora P, et al. The registry of the International Society for Heart and Lung Transplantation: twentieth-sixth official adult lung and heart-lung transplantation report-2009. *J Heart Lung Transpl* 2009;28:1031-49.
- ² Barker AF, Bergeron A, Rom WN, Hertz MI. Obliterative bronchiolitis. *N Engl J Med* 2014;370:1820-8.
- ³ Xu Z, Ramachandran S, Guasekaran M, et al. MicroRNA-144 dysregulates the transforming growth factor- β signaling cascade and contributes to the development of bronchiolitis obliterans syndrome after human lung transplantation. *J Heart Lung Transpl* 2015;34:1154-62.
- ⁴ Charpin JM, Valcke J, Kettaneh L, et al. Peaks of transforming growth factor beta mRNA in alveolar cells of lung transplant recipients as an early marker of chronic rejection. *Transplantation* 1998;65:752-5.
- ⁵ Sheppard D. Transforming growth factor beta: a central modulator of pulmonary and airway inflammation and fibrosis. *Proc Am Thorac Soc* 2006;3:413-7.
- ⁶ Xie T, Liang J, Guo R, et al. Comprehensive microRNA analysis in bleomycin-induced pulmonary fibrosis identifies multiple sites of molecular regulation. *Physiol Genomics* 2011;43:479-87.
- ⁷ Squiers JJ, Arsalan M, Lima B, DiMaio JM. Cerebral protection during deep hypothermic circulatory arrest: can a molecular approach via microRNA inhibition improve on a millennia-old strategy? *J Thorac Cardiovasc Surg* 2015;150:684-6.
- ⁸ Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell* 1993;75(5):843-54.
- ⁹ Ambros V. The functions of animal microRNAs. *Nature* 2004;431:350-5.
- ¹⁰ Fabian MR, Sonenberg N, Filipowicz W. Regulation of mRNA translation and stability by microRNAs. *Annu Rev Biochem* 2010;79:351-79.
- ¹¹ Kurlansky. MicroRNA's: panacea or Pandora's box? *J Thorac Cardiovasc Surg* 2015;150:407-8.