Magnetic Resonance Imaging of Lung Pathology in IL-13 Transgenic Mice

M. D. Silva[1], L. Jose[2], A. Coyle[2], B. Jaffee[2], S. Chandra[1]

[1]Imaging Sciences, Millennium Pharmaceuticals, Inc., Cambridge, MA, United States, [2]Inflammation Pharmacology, Millennium Pharmaceuticals, Inc., Cambridge, MA, United States

INTRODUCTION

Pathological remodeling of airways and parenchymal inflammation are key processes taking place in a number of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). A mouse model of COPD has been developed whereby the overexpression of the cytokine interleukin IL-13 results in a disease phenotype highly reminiscent of COPD, including lung inflammation, mucus metaplasia, protease hyperproduction and subepithelial fibrosis (1). This study demonstrates the sensitivity of non-gated, free-breathing, T_1-weighted magnetic resonance imaging (T_1WI) to this disease phenotype. Signal enhancement presumably from edema, mucus hypersection, and inflammation resulting from pathology induced as a result of the IL-13 transgenic modification provide a robust, pharmaceutical MRI method for the characterization of the COPD disease model for future drug therapy studies.

METHODS

Seven wild-type and seven 8-week-old IL-13 transgenic animals were used to evaluate the MRI. Also, three 17-week-old IL-13 transgenic animals were included for comparison to 8 weeks. Following anesthesia initiation with isoflurane (2% in 1.5 L/min medical air), the animals were transferred to the MRI holder, positioned lying supine, and secured with medical tape. During imaging, animals were freely breathing and no external gating was used to trigger image aquisition. MRI was performed on a Bruker 2.0T, equipped with a 15 cm self-shielded gradient set with ±20 G/cm maximum gradient strength using a home-built, surface RF coil. The surface coil was rectangular with dimensions of 2 cm × 3.5 cm and contoured to match the back of the mouse. T_1WI was performed with a TR of 1000 ms and TE of 9.2 ms. Other parameters include: matrix size = 128 × 128, 10 2-mm-thick transverse slices, FOV = 3 cm × 3 cm, resolution = 0.234 mm × 0.234 mm × 2 mm, NEX = 4, acquisition time = 8 min. MR image analysis and display was performed with Analyze 4.0 (BIR, Mayo Foundation, Rochester, MN, USA; AnalyzeDirect Inc., Lenexa, KS, USA). From a single slice, at the level of the left ventricle, a 12 pixel × 12 pixel region of interest (ROI) was drawn in the dorsal right lobe. A reference 7 pixel × 7 pixel ROI was drawn in the back muscle. The ratio of the lung signal intensity was taken with respect to the muscle signal intensity for comparison across samples. Data is presented as the mean and standard error of the mean for the wildtype and IL-13 transgenic animals, and 2-tailed test was performed to assess the statistical relationship between wild-type and transgenic animals.

RESULTS

Figure 1 shows representative wild-type (left) and IL-13 transgenic (right) MRI. Figure 2 shows the result of the ROI analysis performed on the groups. The ratio of lung-to-muscle signal in the 8-week-old transgenic animals was 93% higher than the age-matched wild-type animals, 0.63±0.07 and 0.33±0.02, respectively (p=0.001). The three 17-week-old animals had a lung-to-muscle signal ratio (0.63±0.05) was statistically different than wild-type (p=0.001) and similar to the 8-week-old transgenic animals (p>0.05) (Fig. 2).

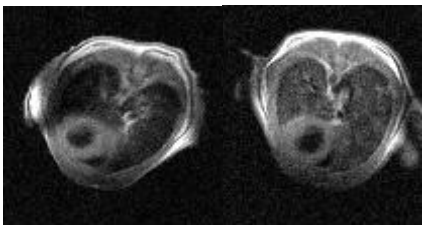

Figure 1 (Left) Images of a wild-type (left) and 8-week-old IL-13 transgenic (right) mouse.

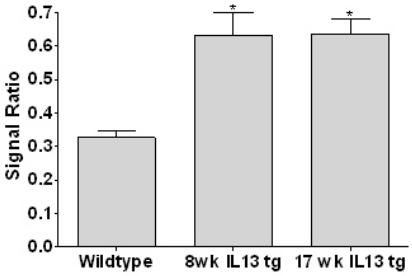

Figure 2 (Right) Graph of the lung / muscle signal ratio. We measured an ratio increase of 93% between wild-type and transgenic animals (p=0.001).

DISCUSSION

The constitutive over-expression IL-13 in these transgenic mice results in a pathological phenotype reminiscent of human COPD: tissue inflammation, mucus hyperproduction, goblet cell hyperplasia, subepithelial airway fibrosis, Charcot-Leyden-like crystal deposition, airway obstruction, and airway hyperresponsiveness. This study demonstrates an MRI method for the study of lung disease in these mice. Figure 1 shows the marked differences between 8-week-old normal and IL-13 transgenic mice. In the normal animals, the lung airspace appears dark on the T_1WI, indicative of the significant air component. The actual signal measured in this area is 2.44(±0.2)-fold higher than background, however, due to the presence of parenchymal tissue. The IL-13 transgenic mice demonstrate a significant hyperintensity in the corresponding lung regions. Comparison to literature and histology indicate that it is most likely due to the inflammation, edema, and mucus hypersection that are hallmarks of the transgene modification, although additional testing is required to determine the true causes of MRI signal changes. The lung MRI signature appears similar between 8 and 17 weeks, however the 17 week sample size is small (n = 3) and must be studied further. In some cases, lung imaging studies are geared towards the visualization of lung parenchyma (2,3) or function contrast-enhanced hyperpolarized gas imaging (4). This study demonstrates, however, that in certain disease cases—such as the IL-13 transgenic mouse—standard imaging methods can be highly effective to visualize the pathology and can enhance existing histological and functional testing methods.

The authors gratefully acknowledge Dr. Jack Elias of Yale University (New Haven, CT) for the IL-13 transgenic model and the valuable contributions of Dr. Christopher H. Sotak, Dr. Karl G. Helmer, and Erica Henning of Worcester Polytechnic Institute (Worcester, MA).

1. Zhu Z et al., J Clin Invest 1999;103:779-788.
2. Bechmann N et al., NMR Biomed 2001;14:297-306.
3. Beckmann N et al., Magn Reson Med 2001;45:88-95.
4. Moller HE et al., Magn Reson Med. 2002 Jun;47(6):1029-51.