Idiopathic Pulmonary Fibrosis and Systemic Sclerosis in Mice

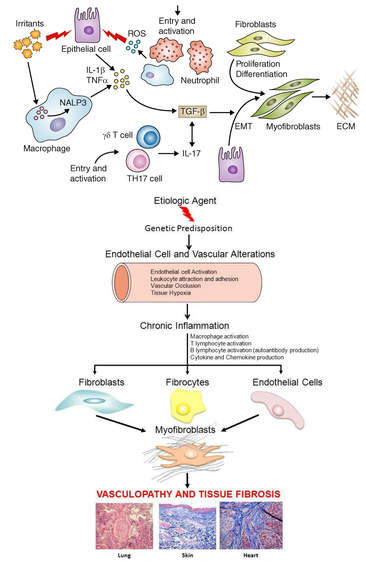
Weiyu Zhang PhD*, Hannah Hendel, Jeremy Drees PhD, Avital Schauder PhD, Ori Brenner DVM, Britnie James PhD

Department of Preclinical Services, MD Biosciences

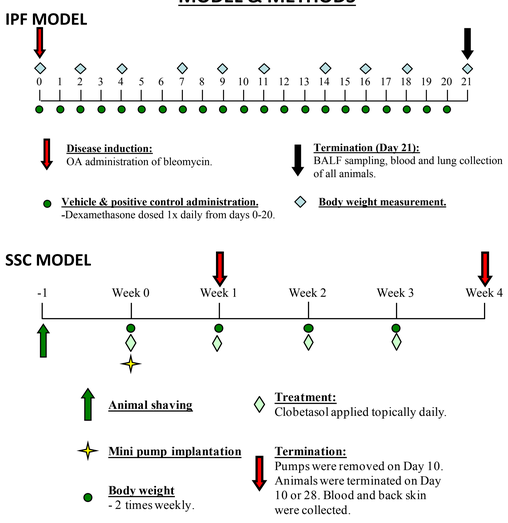
ABSTRACT

Idiopathic pulmonary fibrosis (IPF) and systemic sclerosis (SSc) are fibrotic diseases with poorly understood pathophysiology and minimal treatment options for patients, warranting the need for better preclinical models to help drive drug development. While IPF only effects the lungs, SSc can affect the skin, lungs and other internal organs and both diseases can have poor prognoses after lung function begins to decline. To model these disease in mice, bleomycin (BLM) can be instilled locally to the lung for IPF or systemically through a slow release mechanism for SSc. In the IPF model, similar to humans, significant increases in total protein, pro-fibrotic TGF- β and lymphocyte accumulation into the lungs were observed and accompanied by distorted lung architecture, severe thickening of alveolar walls, and fibrotic nodule development. In the SSc model, dermal thickness and lung toxicity was observed in systemically BLM-induced mice compared to control animals. These data suggest that BLM induced fibrosis, either via local or systemic administration, is an attractive model to analyze the underlying mechanism of fibrosis and test the efficacy of potential therapies.

BACKGROUNDS



MODEL & METHODS



IPF MODEL RESULTS

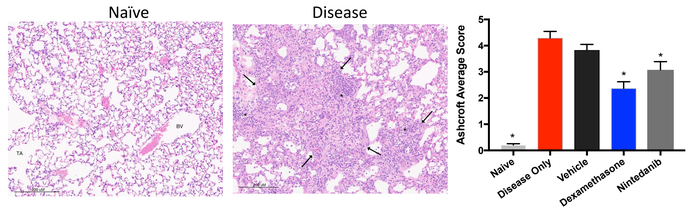


Figure 1. H&E staining of lung tissue. Non-lesioned lung (Naïve): Alveoli/air spaces are open and alveolar walls are thin. Bronchi/bronchioles (Br), terminal airways (TA) and blood vessels (BV) are indicated. Diseased lung: Expansion/replacement of alveolar walls by fibrous tissue (black arrows) is primarily evident toward the hilus adjacent to bronchi/bronchioles (Br). Alveoli/air spaces are obliterated by a mass of fibrous tissue (black arrows) and lymphocyte aggregates (*). * p<0.05 vs Disease only.

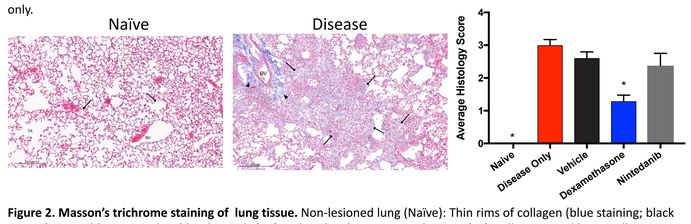
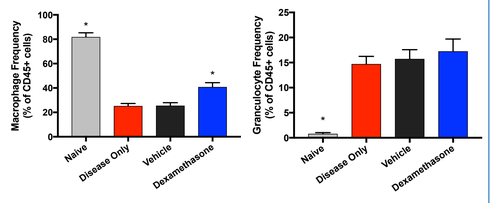


Figure 2. Masson's trichrome staining of lung tissue. Non-lesioned lung (Naïve): Thin rims of collagen (blue staining; black arrows) are visible surrounding blood vessels (BV) and in alveolar or terminal airway (TA) walls. Diseased lung: Collagen expanding alveolar walls stains blue with trichrome (black arrows). Endogenous collagen (black arrowheads) surrounds blood vessels (BV). * p<0.05 vs Disease only.



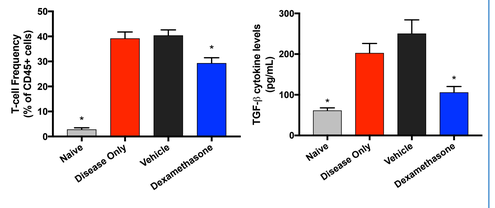
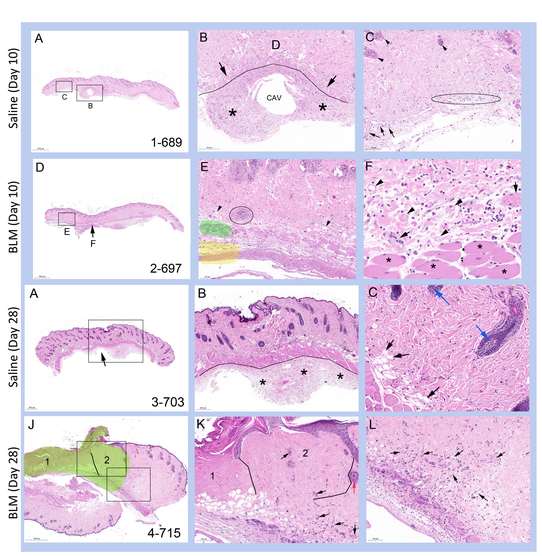
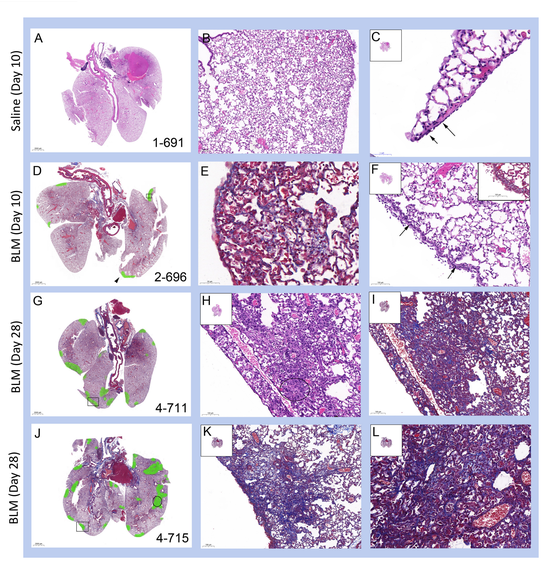


Figure 3. Inflammatory cellular infiltration and level of TGF-b in bronchoalveolar lavage fluid (BALF). * p<0.05 vs Disease only.

SSc MODEL RESULTS





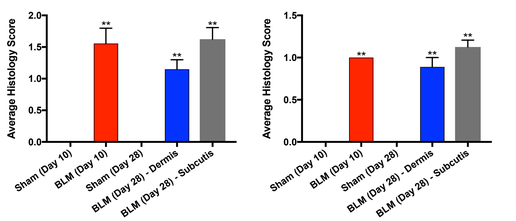


Figure 4. Representative microscopic findings in skin. Histopathological analysis of skin sections showed mild to moderate inflammation, edema and fibrosis at 10 days of bleomycin administration. At 28 days, skin samples show similar lesions of full thickness coagulative necrosis, including condensed collagen with reactive changes, such as inflammation, fibroblast hypertrophy and hyperplasia and proliferation. ** p<0.01 vs sham.

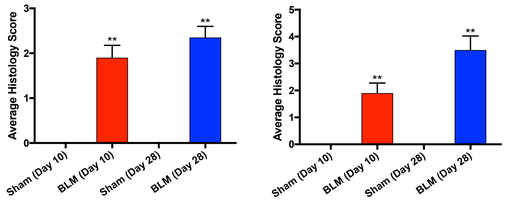


Figure 5. Representative microscopic findings in lung. On day 10, most samples show small segments of mild pleural fibrosis and mild hypercellularity due to mesothelial hyperplasia, alveolar histioctyosis and mononuclear infiltration. On day 28, fibrosis and inflammation are found in 10%-50% of the lungs, however mainly in limited extent. ** p<0.01 vs sham.

SSc MODEL RESULTS

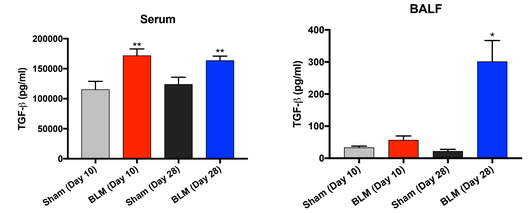


Figure 6. Level of TGF-β in serum and bronchoalveolar lavage fluid (BALF). * p<0.05, ** p<0.01 vs sham.

CONCLUSIONS

- **Idiopathic Pulmonary Fibrosis**
  - Bleomycin induced IPF via oral aspiration.
  - Characteristics include BLM-induced epithelial cell death, excessive inflammatory infiltrate (days 0-7), and ultimately activation of fibroblasts and development of fibrosis (days 10-21).
  - Disadvantages: Rapid onset, preceding inflammation, and self-resolution past 21 days.
  - The American Thoracic Society recommended the BLM-induced IPF model in C57BL/6 mice via oropharyngeal administration.
- **Systemic Sclerosis**
  - Systemic sclerosis was induced via continuous delivery of Bleomycin in osmotic pump .
  - Characteristics include stable dermal inflammation and fibrosis with extensive and reproducible interstitial lung disease in mice.
  - Elevated TGF-β, the primary factor that drives fibrosis in blood and lung.
  - Advantages: Convenient without need of repetitive procedure; low mortality; stable disease model.
  - Disadvantages: Species dependent and mild disease.

❖ **In total these data suggest that Bleomycin induced fibrosis, either via local or systemic administration, is an attractive model to analyze the underlying mechanism of fibrosis and test the efficacy of potential therapies.**

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MD Biosciences, Inc.
Imation Place
Oakdale, MN 55128

Our Phone
(888) US-MDBIO
(651) 641-1770

Email / Website
Info-us@mdbiosciences.com
http://www.mdbiosciences.com