Mouse Models of Inflammatory Lung Diseases

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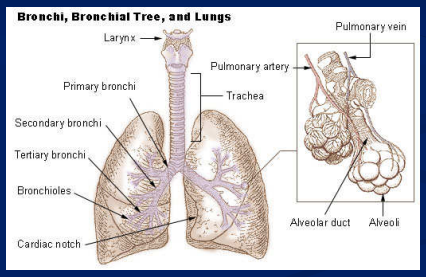
Outlines

- Basic lung structure, function, and inflammatory lung diseases
- Methods, techniques, and approaches to studying lung diseases
- Mouse models of inflammatory lung diseases

Lung: Basic Structure

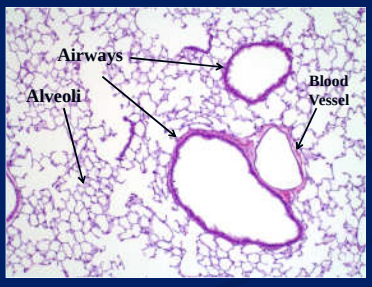
Anatomy



From Wikipedia

Lung: Basic Structure

Lung Histology H&E (100x)



Lung Function and Diseases

- Gas exchange: O_2 from atmosphere to bloodstream and CO_2 from bloodstream to atmosphere
- Diseases
  - COPD
  - Asthma
  - Pneumonia
  - Pulmonary fibrosis
  - Sarcoidosis
  - Cystic fibrosis
  - Lung cancer
  - …

Studying the Lung: Methods and Techniques

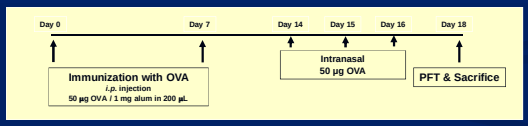
- Pulmonary Function Test (PFT)
  - Airway resistance
  - Lung compliance
- Bronchoalveolar Lavage (BAL)
  - Inflammatory cells in the airway: total and differential
  - Mediators: cytokines, chemokines
- Lung tissues
  - Histology: H&E, Alcian Blue, PAS, Trichrome
  - Proteins
  - RNA
  - Immunohistochemistry (IHC)
  - FACS analysis of cell populations
  - Culture of specific cell types

Studying the Lung: Approaches

- Stimulation
  - Allergens
  - Cigarette smoke
- Transgenics
  - Inflammatory cytokines
- Knock-out & knock-in
  - Cytokines & receptors
  - Siglecs
- Mutant strains
  - Phosphatases

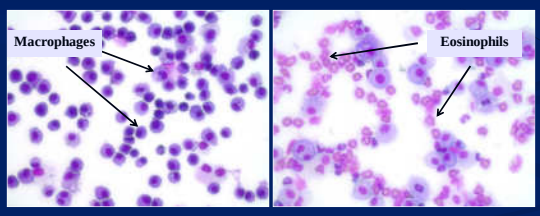
Allergen Induced Allergic Asthma

Protocol for ovalbumin (OVA) induced allergic asthma



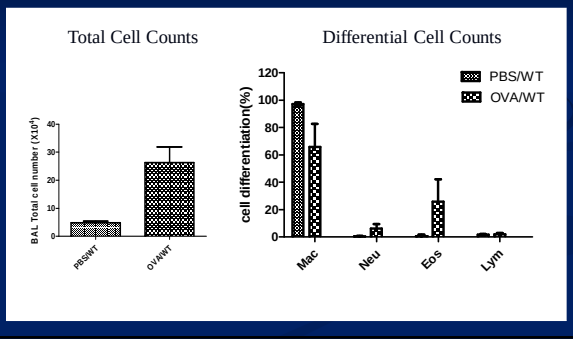
OVA Induced Airway Inflammation

BAL Cells



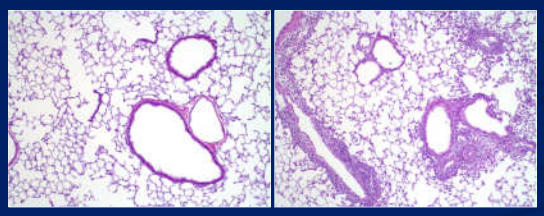
PBS OVA

OVA Induced Airway Inflammation



OVA Induced Lung Inflammation

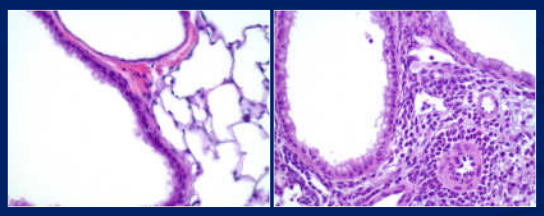
H&E (100x)



PBS **OVA**

OVA Induced Lung Inflammation

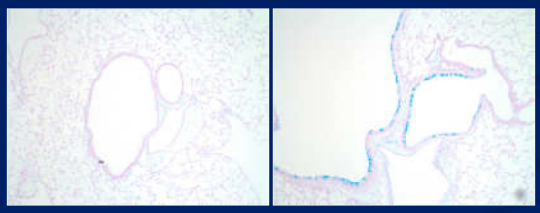
H&E (400x)



PBS **OVA**

OVA Induced Lung Inflammation

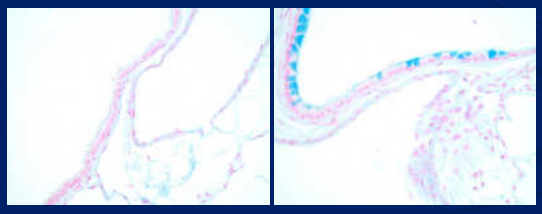
Alcian Blue (100x)



PBS OVA

OVA Induced Lung Inflammation

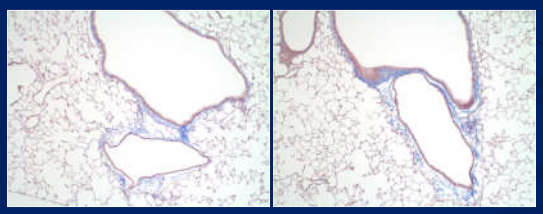
Alcian Blue (400x)



PBS OVA

OVA Induced Lung Inflammation

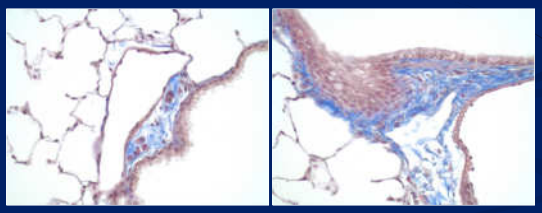
Trichrome (100x)



PBS OVA

OVA Induced Lung Inflammation

Trichrome (400x)



PBS **OVA**

Elastase Induced Emphysema

Protocol for elastase induced emphysema

Porcine Pancreatic Elastase

1u/mouse, I.T. once

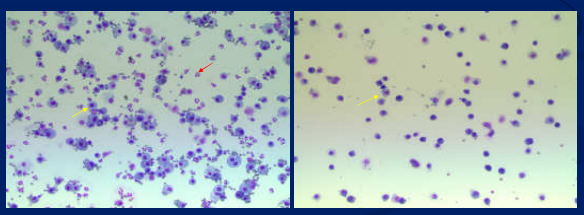
Sacrifice &

Collect BAL, lung tissue

Elastase Induced Airway Inflammation

BAL Cells

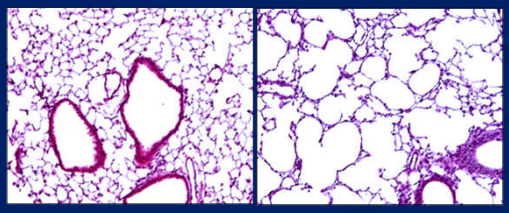
Day 2 **Day 21**



Elastase Induced Emphysema

Lung Histology (H&E 20x)

Day 3 Day 21

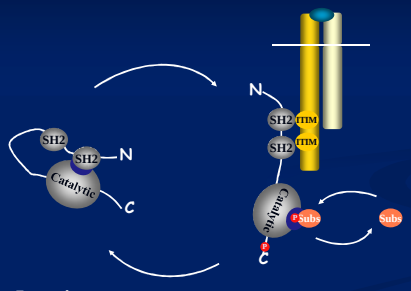


SHP-1

Src **H**omology 2 domain-containing protein tyrosine **P**hosphatase-**1**

Encoded by the *hcp* gene
Primarily expressed in hematopoietic-derived cells
Negative regulator of a variety of growth factor/cytokine signaling pathways
Activated SHP-1 → binds to its target proteins → dephos-phorylates the phospho-tyrosine residues → terminates the signaling

SHP-1 Regulation of Signaling



Inactive **Active**

SHP-1 Deficiency in Mice

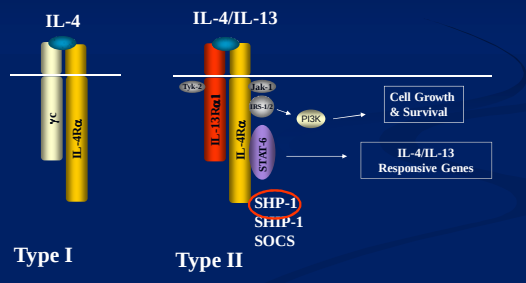
- Motheaten mice (*me/me*) – a natural mutant strain
- Viable motheaten mice (me^v/me^v) – another spontaneous mutant strain

⇒ The mutations cause aberrant splicing of the SHP-1 transcript, resulting in diminished production of functional SHP-1 protein

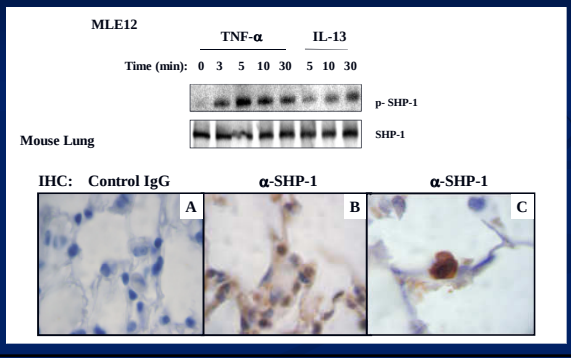
- Phenotype

inflammatory lesions of the skin, increased neutrophils in the peripheral blood, glomerularnephritis, abnormal lymphoid tissues, pneumonitis with macrophage infiltration in the alveoli, increased production of immunoglobulins, depressed immune responses, profound NK-cell deficiency, and a shortened life span (average 22 days and 61 days, respectively)

IL-4/IL-13 Signaling Systems



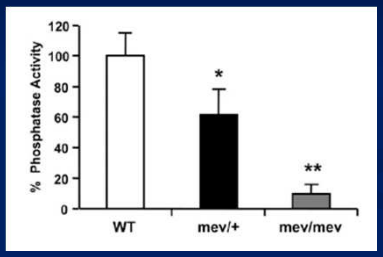
SHP-1 Expression and Activation in Lung Epithelial Cells



Hypothesis

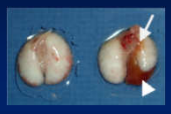
SHP-1 is an important regulator of
- **Immunological homeostasis of the lung**
- **Allergic inflammatory responses**

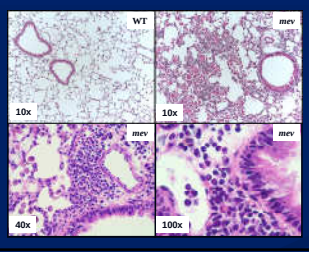
SHP-1 Deficiency and Phenotype

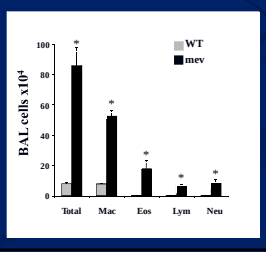


***mev/+*: Phenotypically Normal**
***mev/mev*: Inflammatory phenotype**

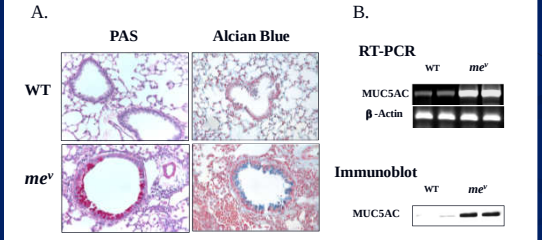
Pulmonary Inflammation



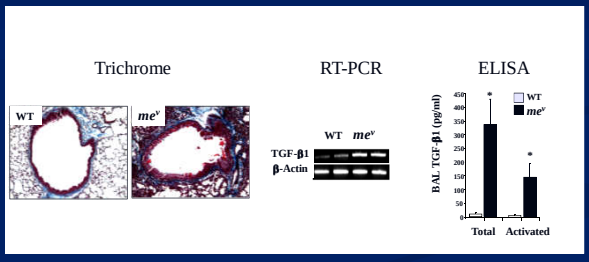




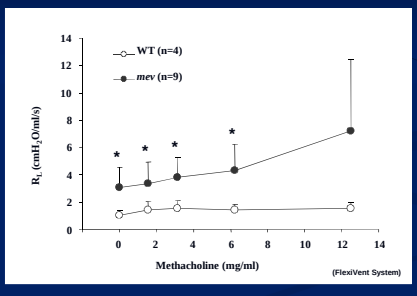
Mucus Hyperproduction



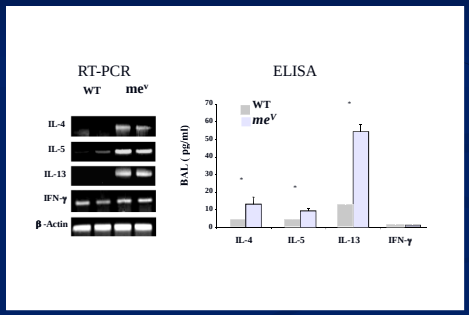
Pulmonary Fibrosis



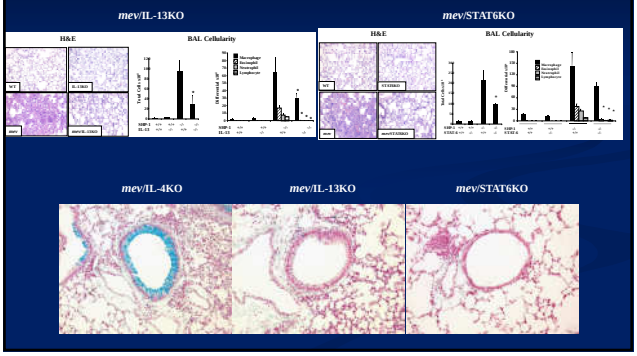
Airway Resistance and Hyperresponsiveness



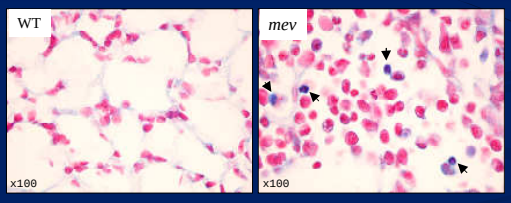
Upregulation of Th2 Cytokines



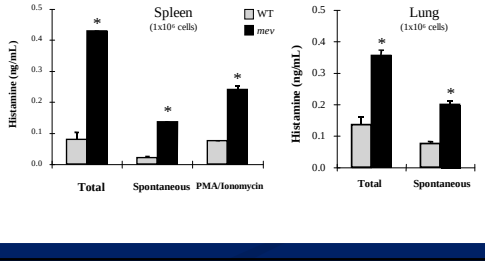
Role of Th2 Cytokines in Pulmonary Inflammation



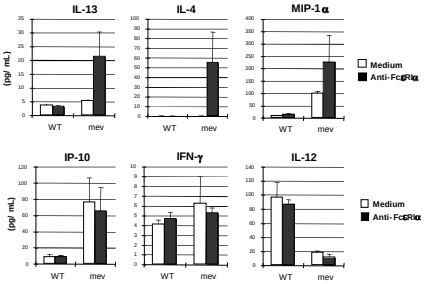
Increased Mast Cells in the Lung



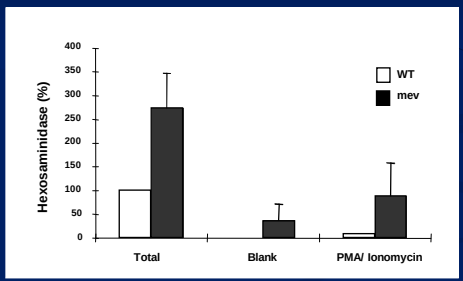
Histamine Content and Release



Cytokine Production by Splenocytes

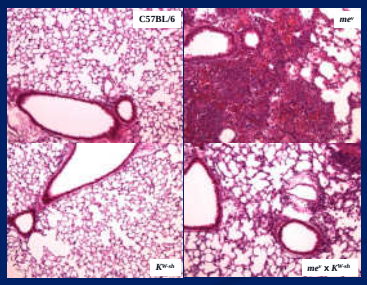


Hexosaminidase Content and Release by BMMC



Mast Cells and Lung Inflammation

Crossbreeding to mast cell deficient $K^{w\text{-}sh}$ mice



Summary

mev mice:

- Spontaneous and progressive pulmonary inflammation rich in macrophages, lymphocytes, and eosinophils
  - ↑ Th2 cytokines IL-4, IL-5, and IL-13
  - ↑ Th2 chemokines Eotaxin and MCP-1
- Mucus hyperplasia ↑ Mucin genes
- Subepithelial and parenchymal fibrosis ↑ TGF-β
- Increased airway resistance and AHR
- Mast cell-dependent