A new short-term mouse model of chronic obstructive pulmonary disease identifies a role for mast cell tryptase in pathogenesis

Beckett EL et al.
J Allergy Clin Immunol (2013 Mar;131(3):752-762)

Denise Traxler-Weidenauer
Animal models for COPD

- there has been no useful small-animal model for COPD so far
  - single-factor approaches
  - acute models which do not evaluate long-term smoke induced inflammatory responses
  - chronic models of more than 6 months duration
- LPS & elastase in rodents induce COPD-like lung damage
- short-term models do not result in emphysema or a decline in lung function
- chronic models induce only mild alterations in lung function
Mast cells

- secretion granules contain: histamine, proteases, heparin
- stimulated via IgE
- relevance in COPD:
  - increased in inflammatory infiltrates
  - htryptase-β levels in sputum correlate with severity
  - exposure of MCs to cigarette smoke-treated culture medium increases mMCP-6 expression
  - mMCP-6 promotes inflammation, chemokine expression and macrophage & neutrophil chemotaxis

Junquiera LCU et al. (2003)
Beckett EL et al. (2013)
www.nhs.uk (February 28th, 2013)
Methods

- WT BALB/c, WT C57BL/6 & mMCP-6−/−
- nose-only exposure for 1 - 12 weeks
- 24 cigarettes per day, 5 times per week
Methods

- airway inflammation: inflammatory cells in BALF
- parenchymal inflammation: histology, qPCR
- macrophage & mast cell numbers: flow cytometry & histochemistry
- airway remodelling: number of goblet cells & airway epithelial thickening
- emphysema: mean linear intercept technique
- lung function
Methods

- glucocorticoid treatment: Dexamethason 3 times per week
- respiratory tract infections
  - streptococcus pneumoniae
  - influenza virus
  - culture or plague assays of lung homogenates
- macrophage depletion: liposome-encapsulated clodronate
Methods

- tryptase-treated macrophages
  - B6 mouse bone marrow-derived macrophages
  - recombinant htryptase-β
  - evaluation of TNF-α, Cxcl1/keratinocyte chemokine & IL-1β transcripts
Results

Beckett EL et al. (2013)
Results

![Graph showing MSCs fold change from control over time: 4wk, 6wk, 8wk, 12wk. The graph indicates significant differences at certain time points.](image1)

![Graph showing epithelial area (μm²/μm²) over time: 4wk, 6wk, 8wk, 12wk. The graph indicates significant differences at certain time points.](image2)

![Graph showing alveolar diameter (μm) over time: 4wk, 6wk, 8wk, 12wk. The graph indicates significant differences at certain time points.](image3)

![Images showing control (Ctrl) and Smk conditions over time: 4wks, 6wks, 8wks, 12wks.](image4)
Results

8 weeks of smoking exposure induces characteristic features of COPD in mice

- Increased levels of transcripts that encode TNFalpha, Cxcl1, IL-1beta
- Increased cellular infiltrates in parenchyma
- Increased numbers of mucus secreting goblet cells
- Chronic inflammation (increases in macrophages, neutrophils & lymphocytes)
- Alveolar enlargement
- Airway epithelial thickening

Beckett EL et al. (2013)
Results

Beckett EL et al. (2013)
Results
Results

A. Cells/ml BALF (x10^4)

B. Alveolar diameter (μm)

C. Work of breathing (arbitrary units)

D. TLC (ml)

E. FRC (ml)

F. FEV1/FVC
Results
Results

Beckett EL et al. (2013)
Results

Beckett EL et al. (2013)
Results

Beckett EL et al. (2013)
Discussion

• new short-term mouse model for COPD
  • covering many features characteristic for COPD
  • time-consuming
• macrophages (stimulated by mast cell tryptase) seem to play an important role for developing COPD
  • macrophage depletion & knockout of mMCP-6 lead to reduced disease severity