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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

February 2013

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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

Beckett EL et al. (2013)

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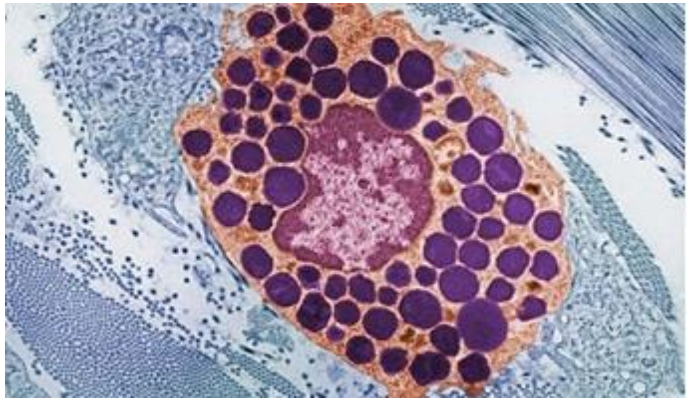
Mast cells

- 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)*

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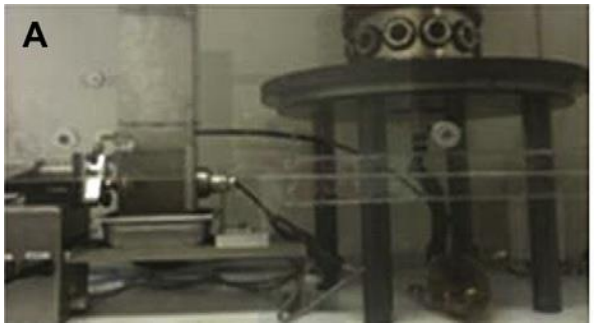
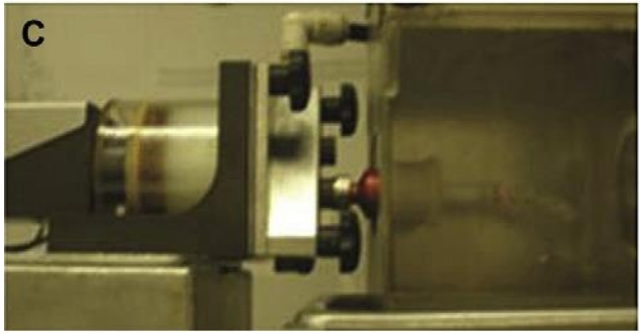
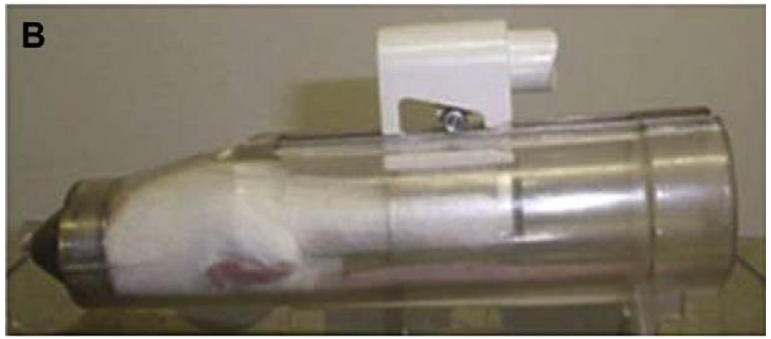
Methods

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







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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

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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

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Methods

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

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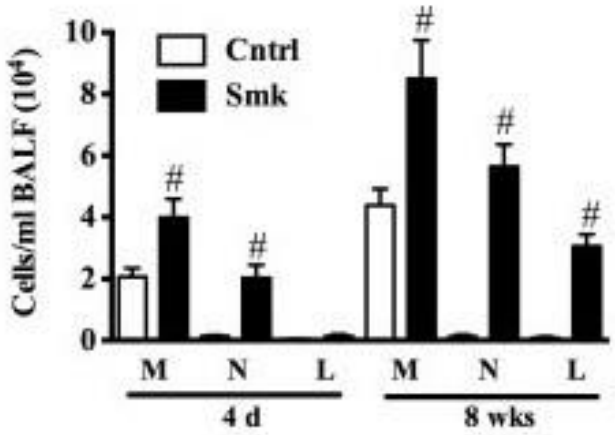
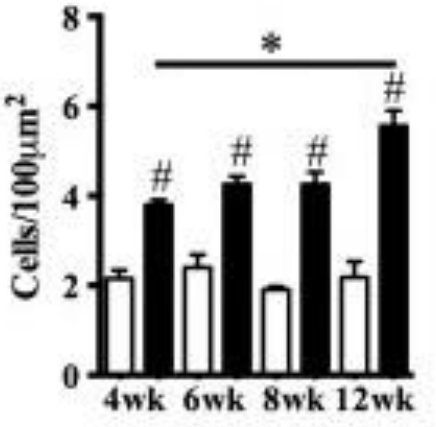
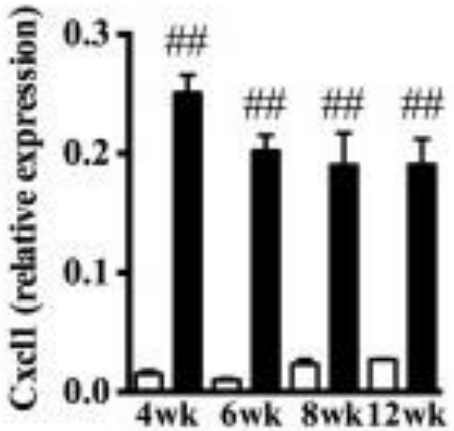
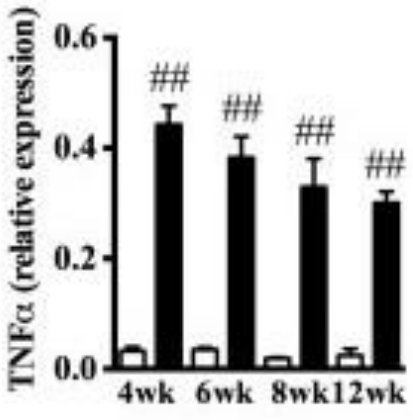
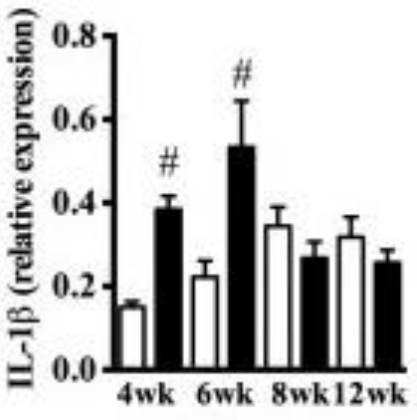
Results











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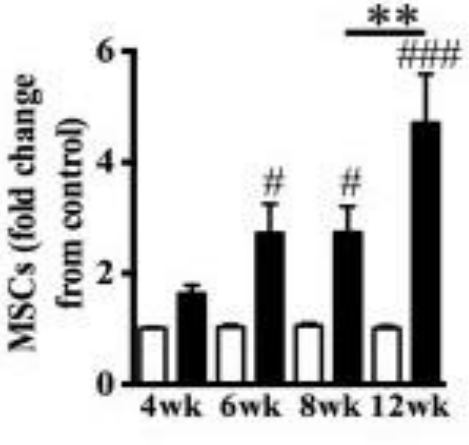

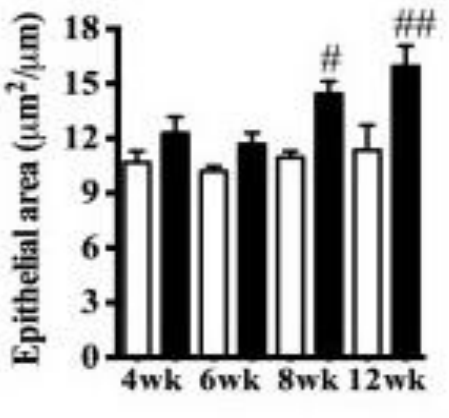

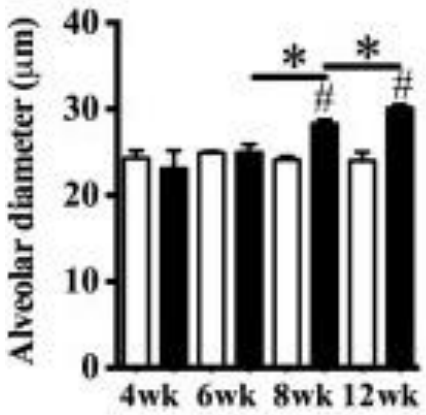

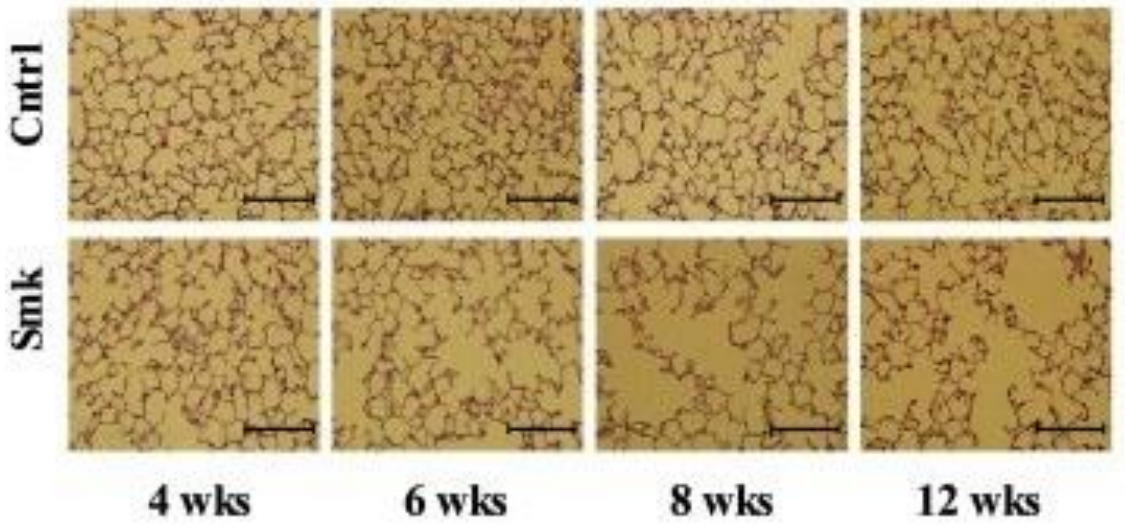

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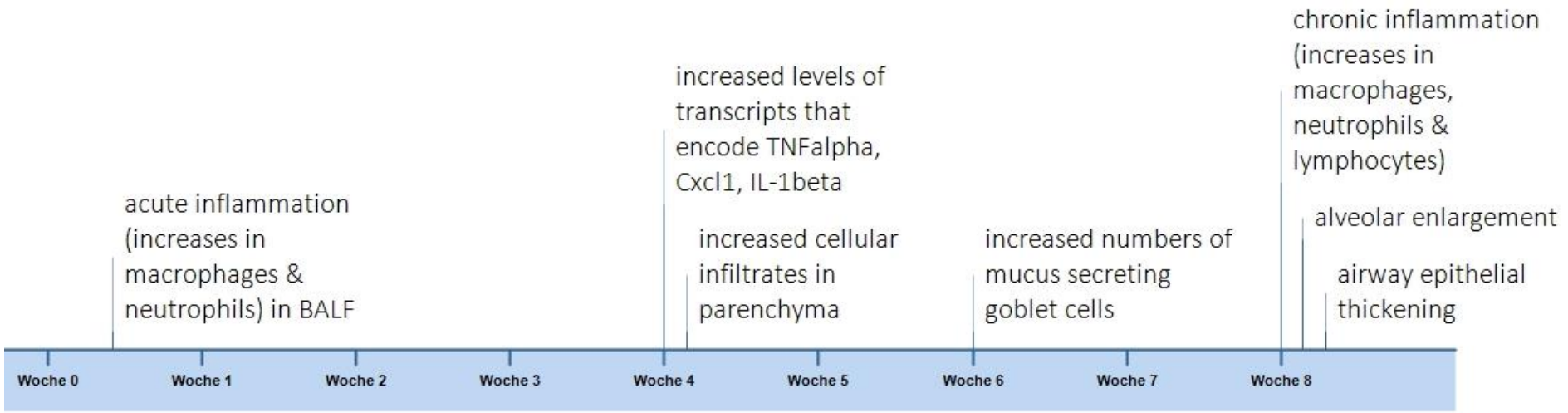

8 weeks of smoking exposure induces characteristic features of COPD in mice

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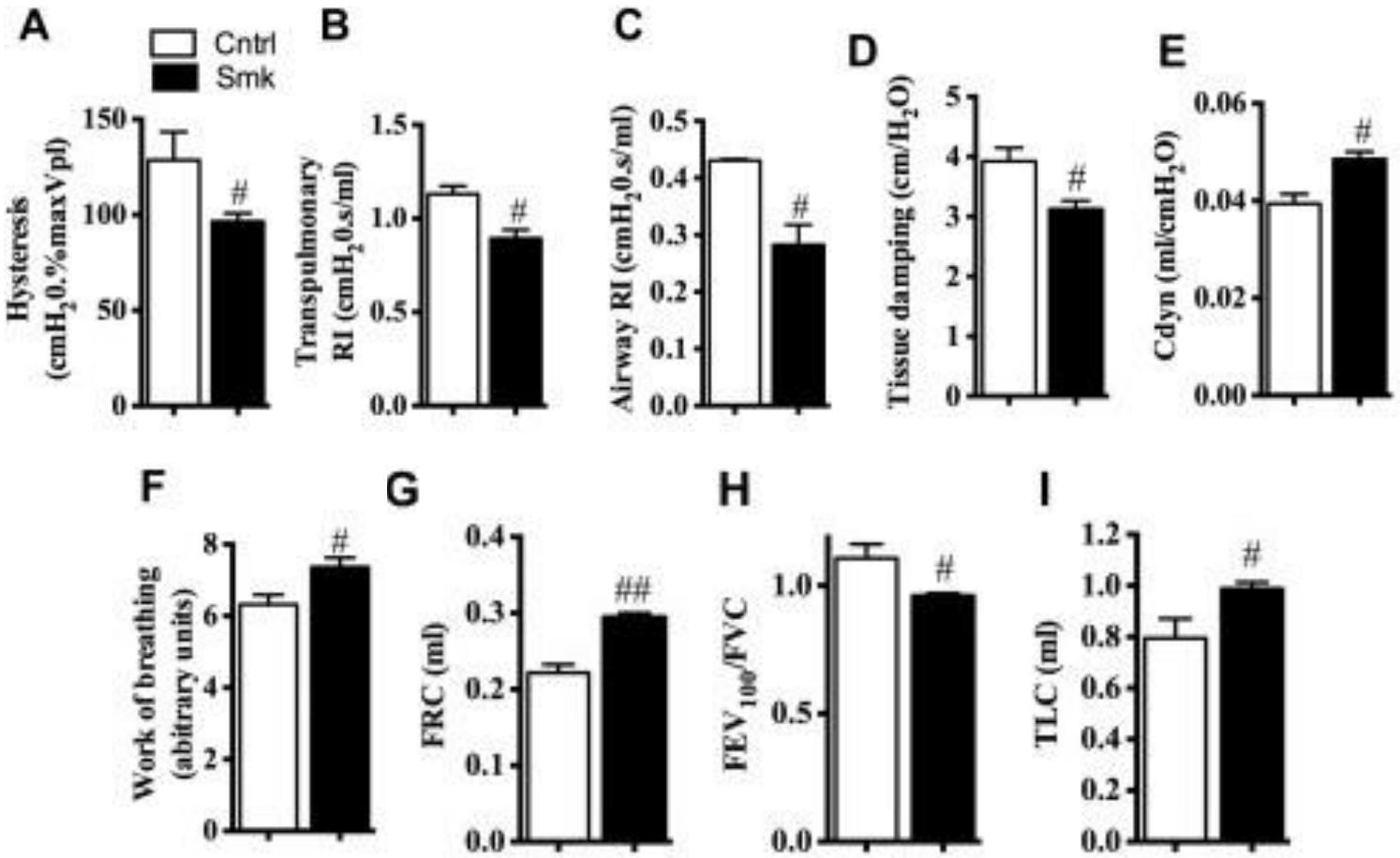

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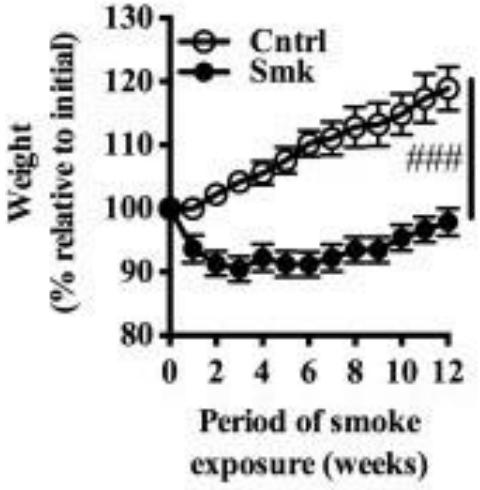

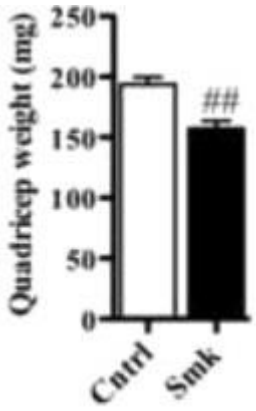

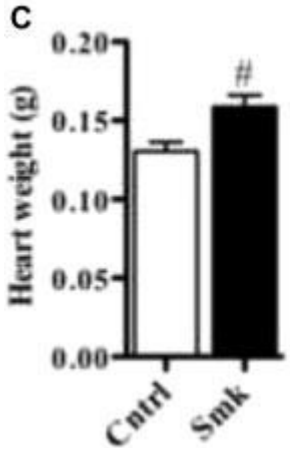

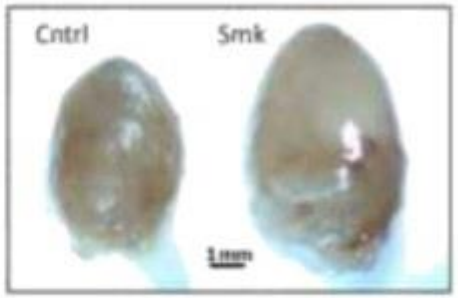

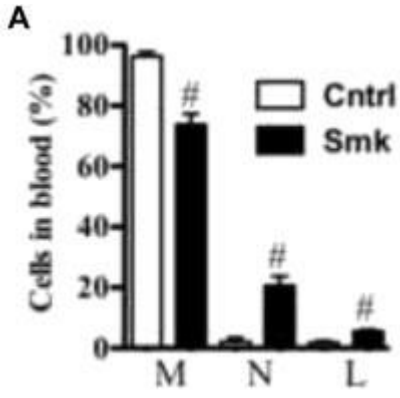

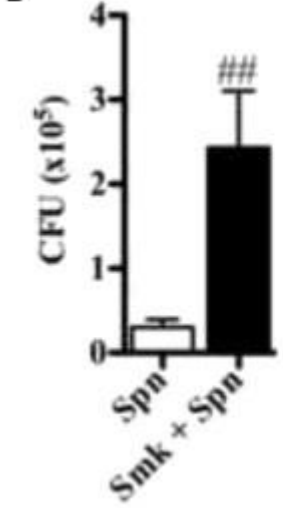

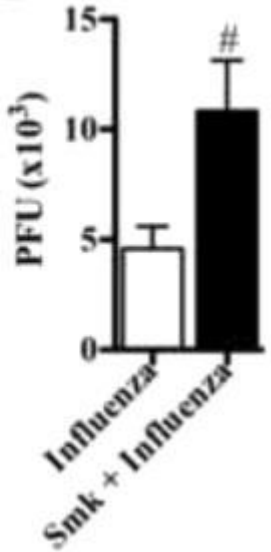

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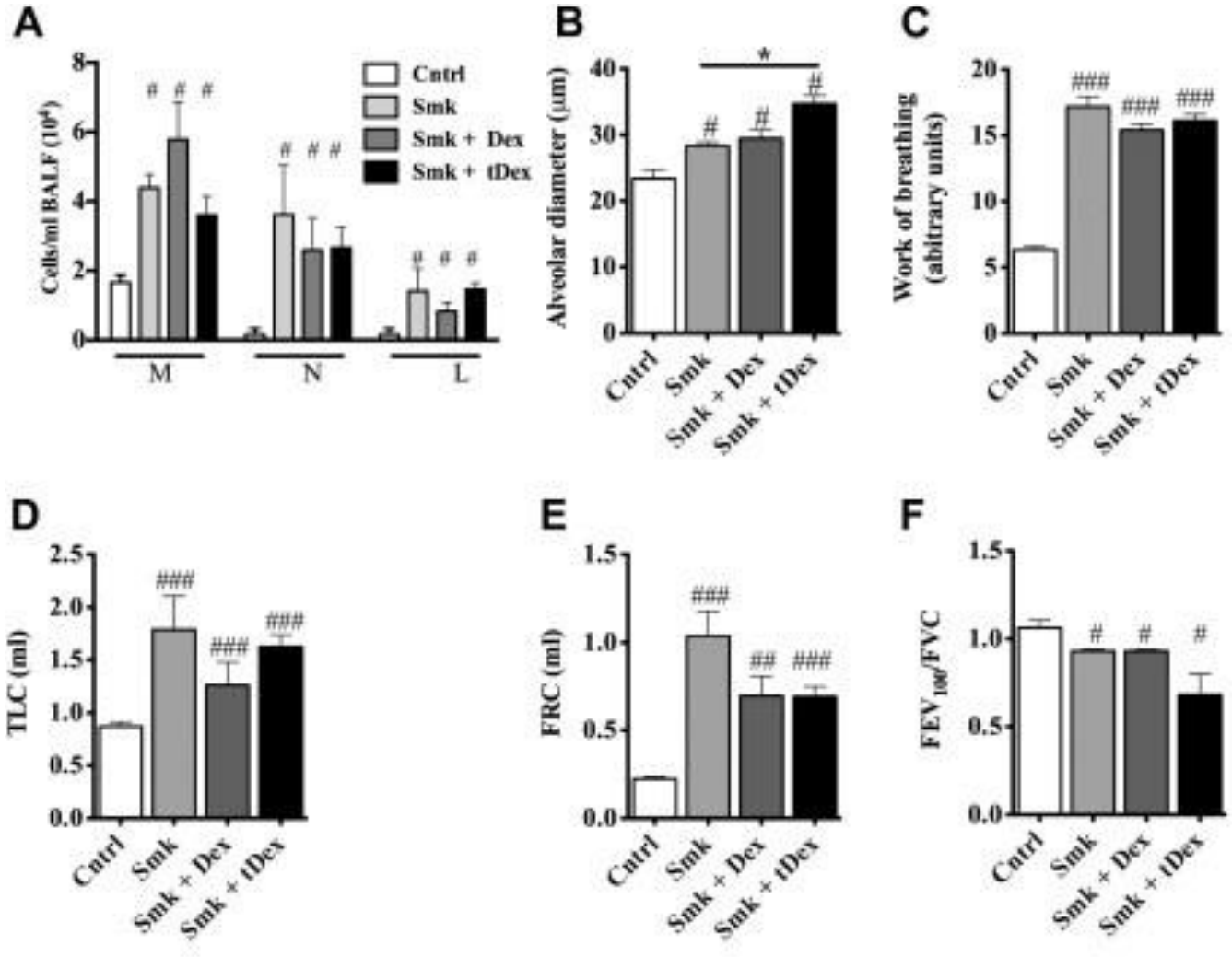

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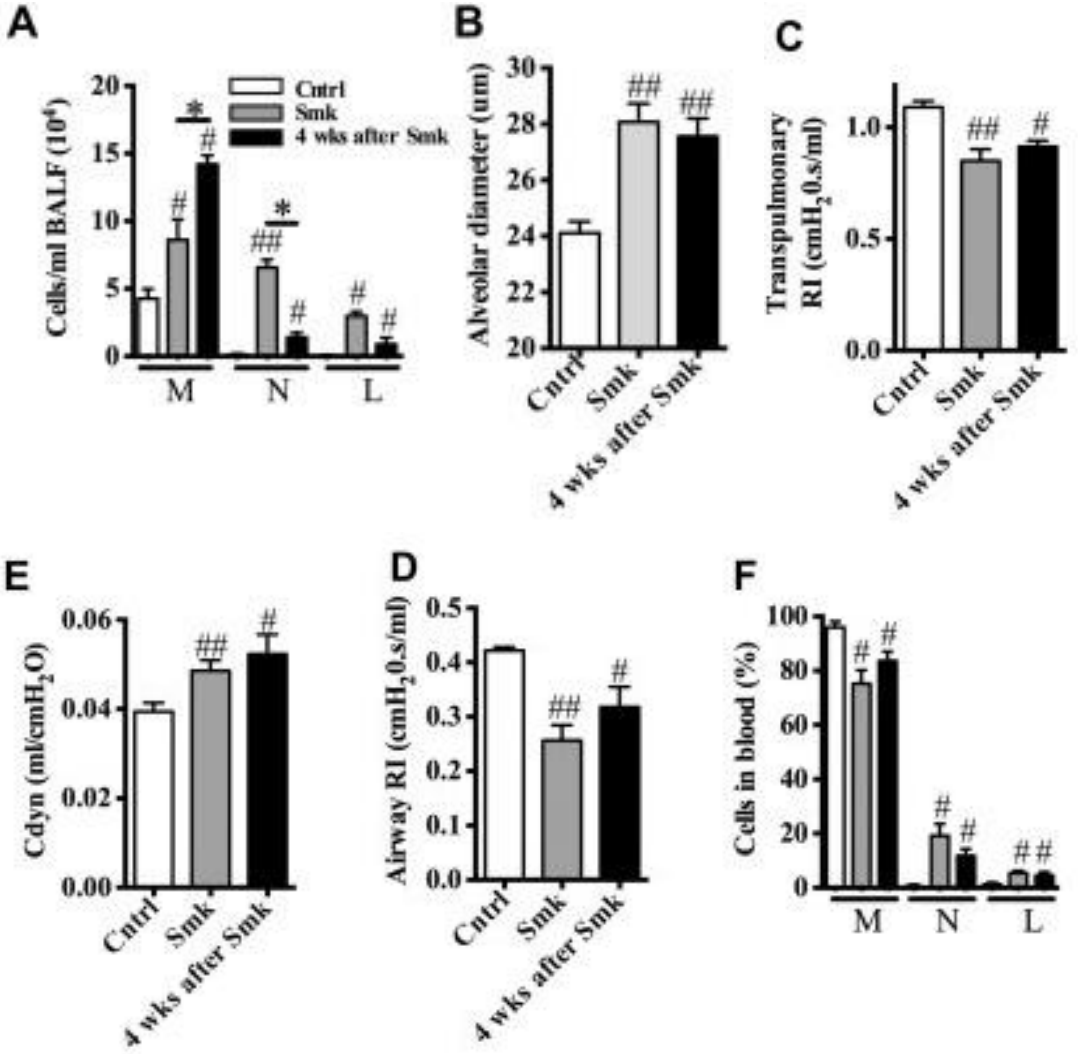

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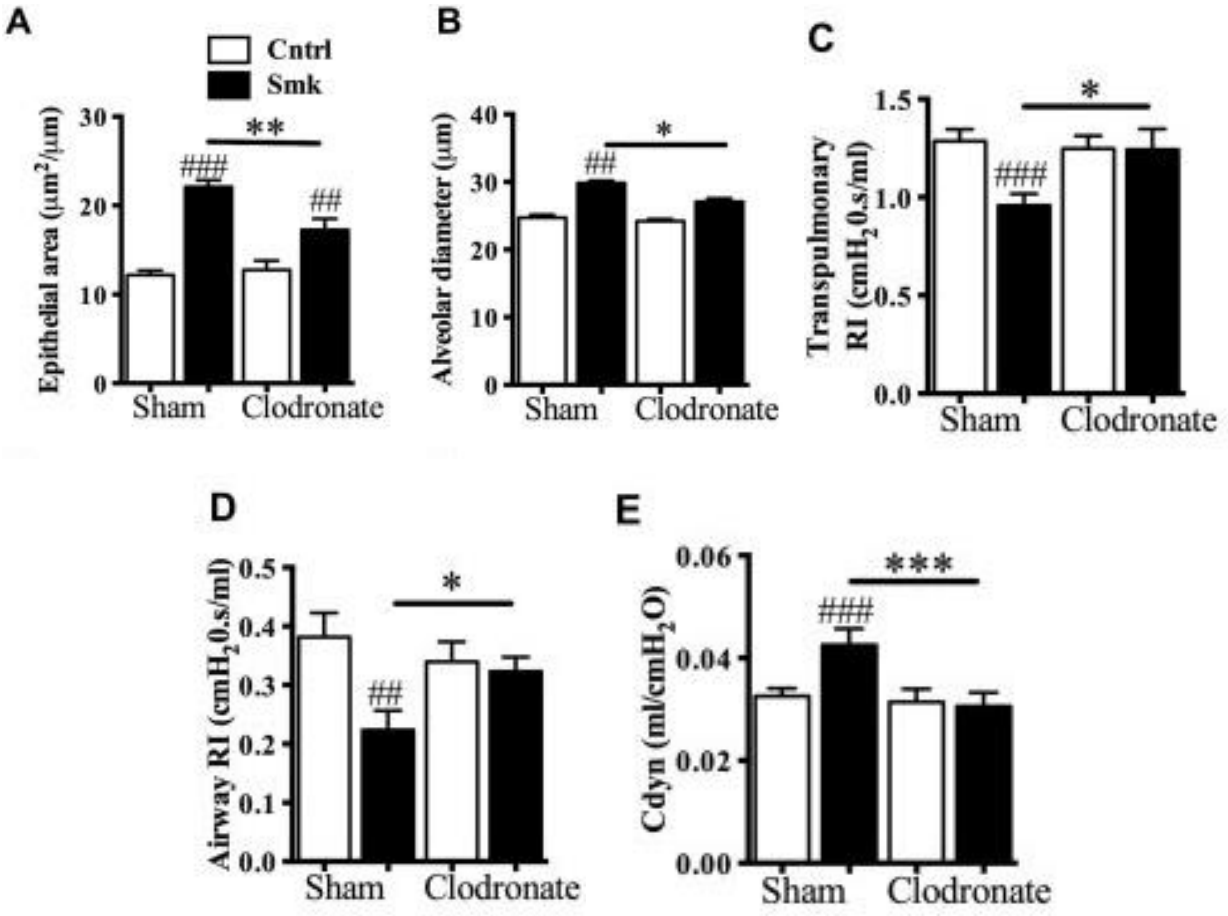

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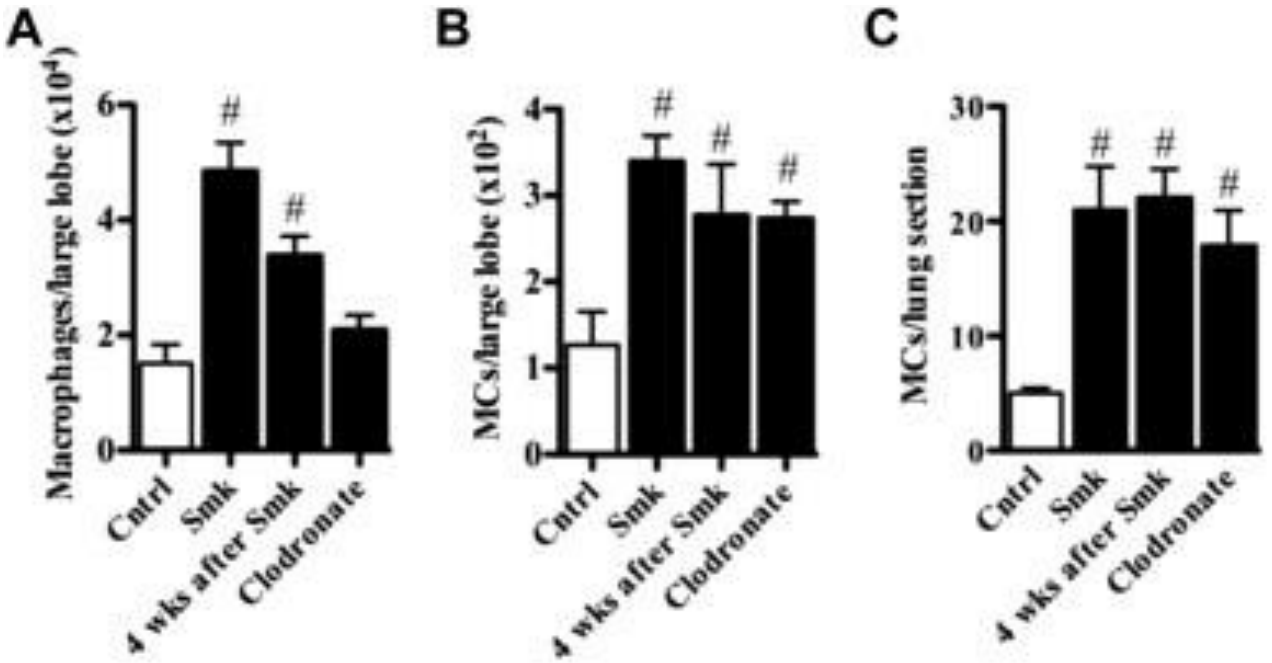

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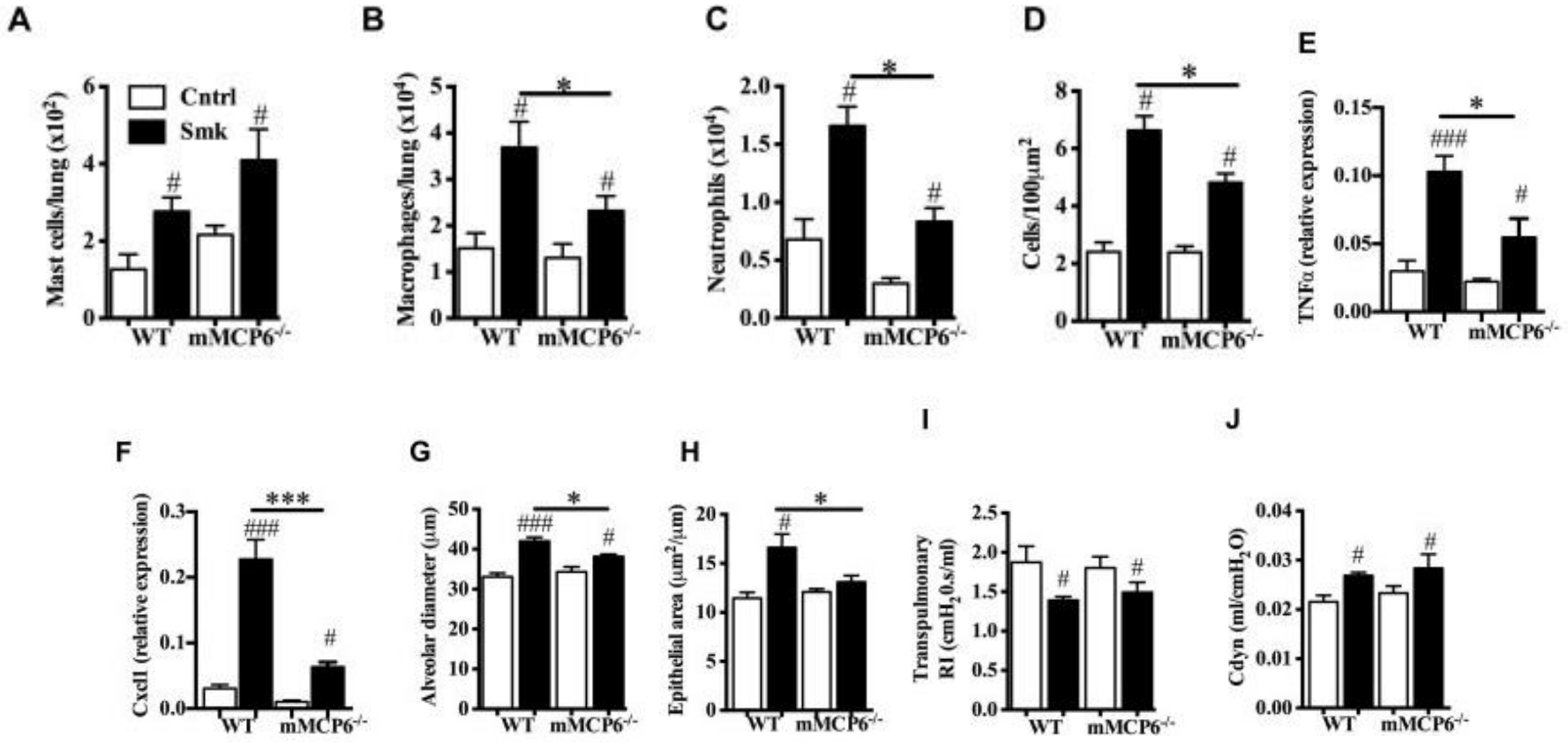

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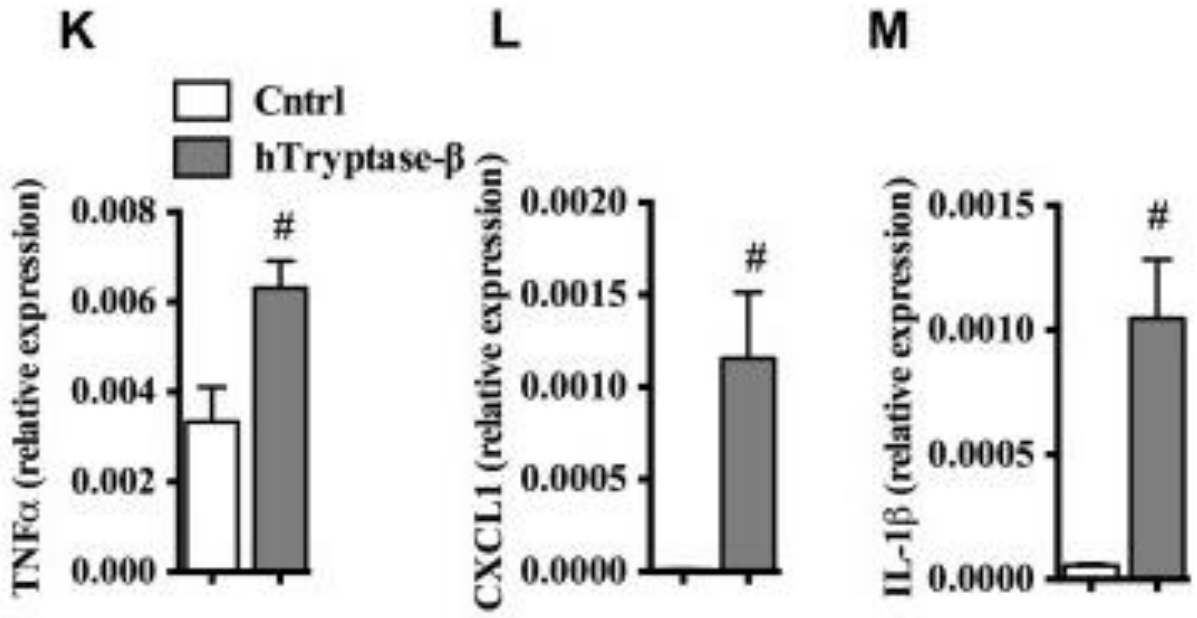

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Discussion

- 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

Beckett EL et al. (2013)