Airway Inflammation and Remodeling

David Ramos Barbón, MD, PhD

Consultant Respiratory Physician

Hospital de la Santa Creu I Sant Pau, Barcelona

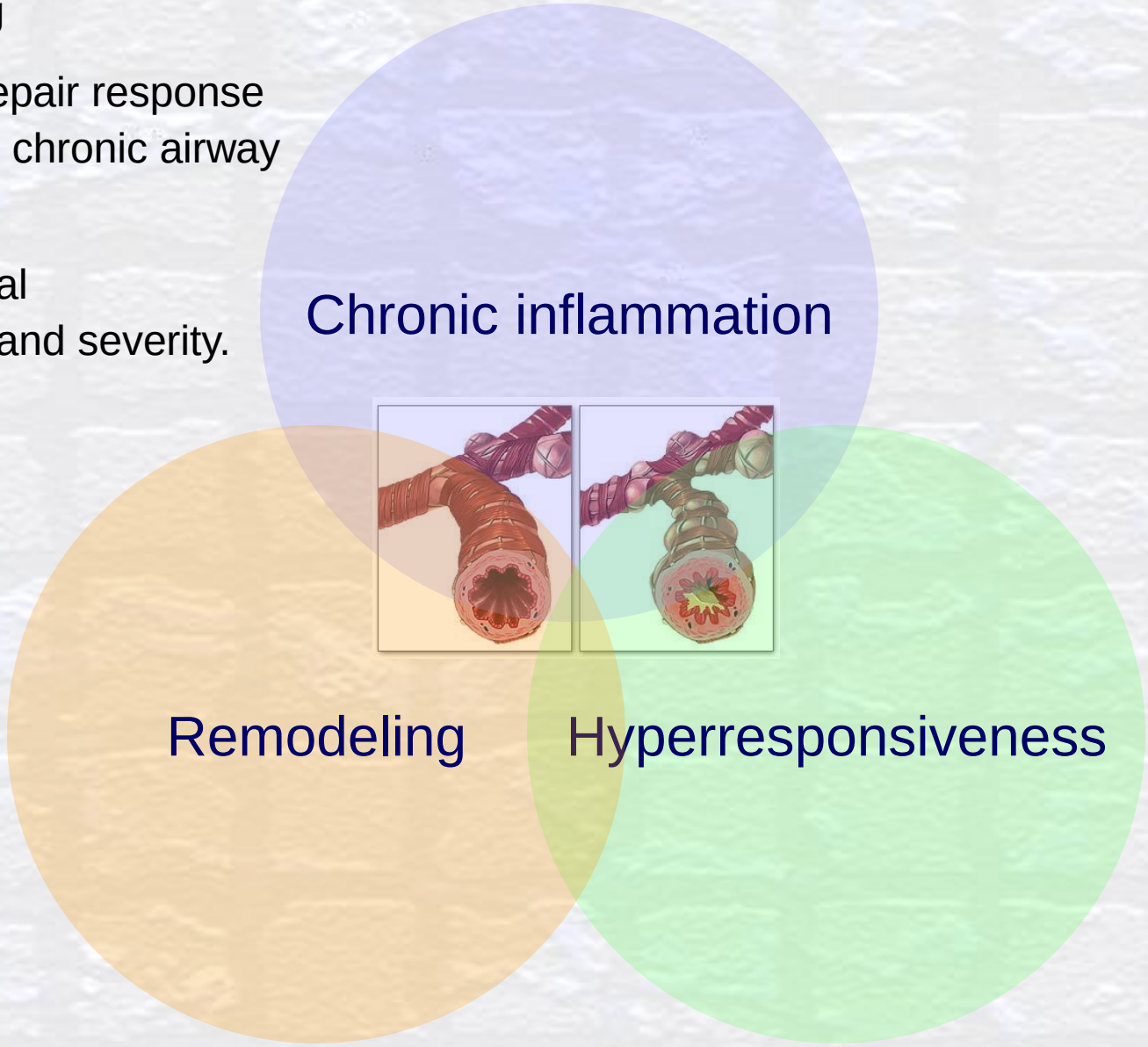
HOSPITAL DE LA SANTA CREU I SANT PAU

UNIVERSITAT AUTÒNOMA DE BARCELONA

Institut sant pau

Asthma physiopathological substrate: remodeling

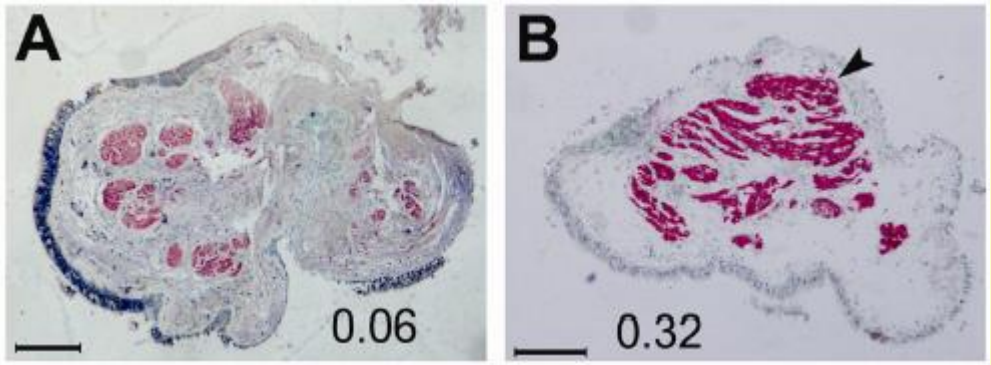
- **Airway remodeling**
  - Dysregulated repair response associated with chronic airway inflammation.
  - Underlies clinical manifestations and severity.

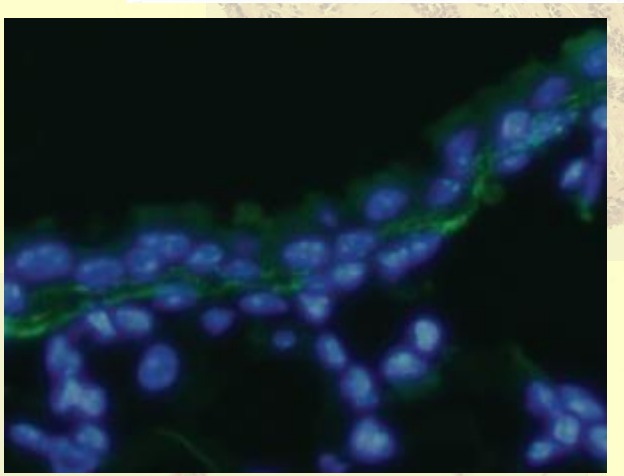


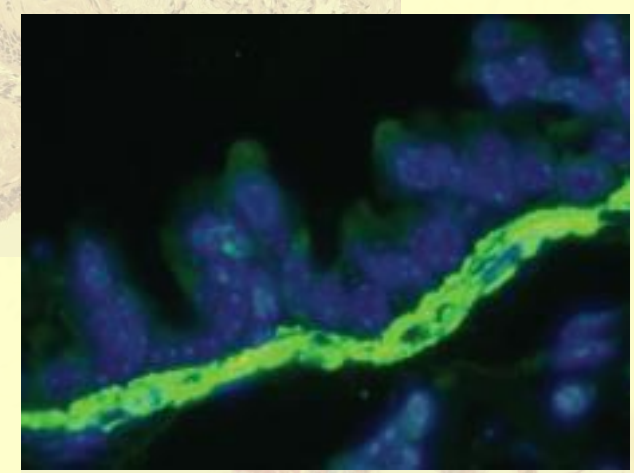
Airway remodeling components

Mucous metaplasia

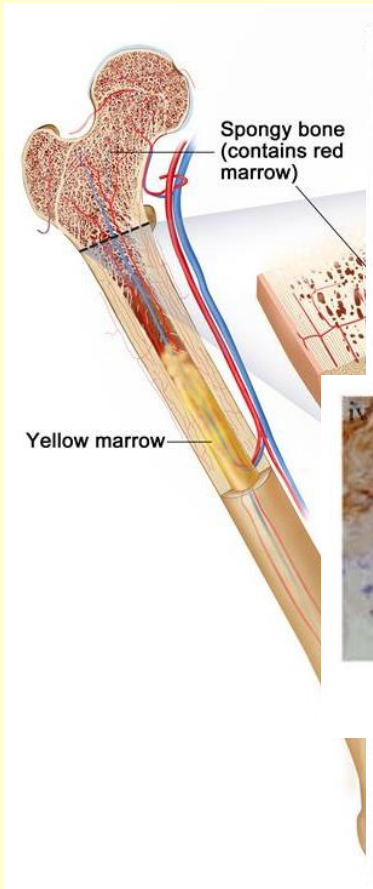
Airway smooth muscle hyperplasia/hypertrophy

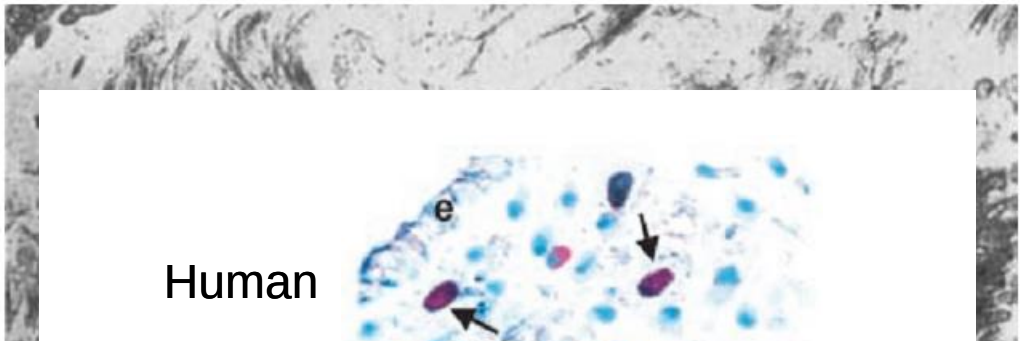


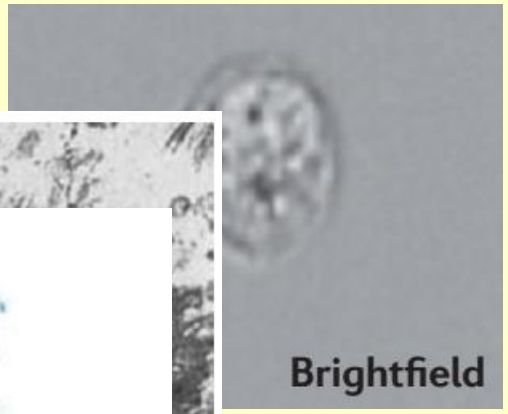




Fibrocytes

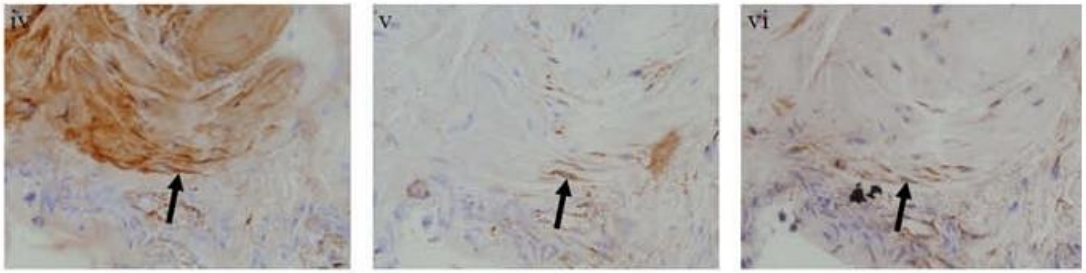






Rev Immunol 2011;11:427-35

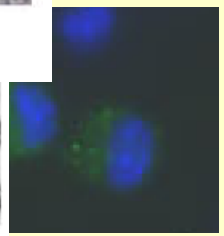
Human



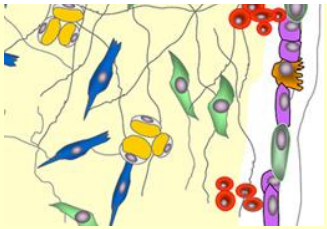
Saunders R et al. *J Allergy Clin Immunol* 2009;123:376-384

Schmidt M et al. *J Immunol* 2003;171:380-389

al stem cells



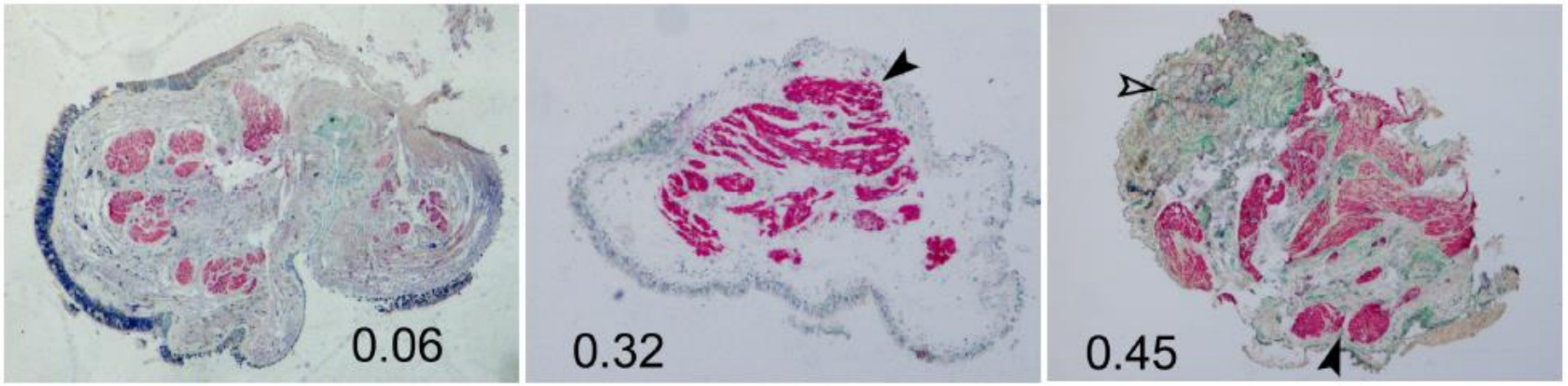
ruo L et al. *Allergy* 2014;69:730-40



Stroma

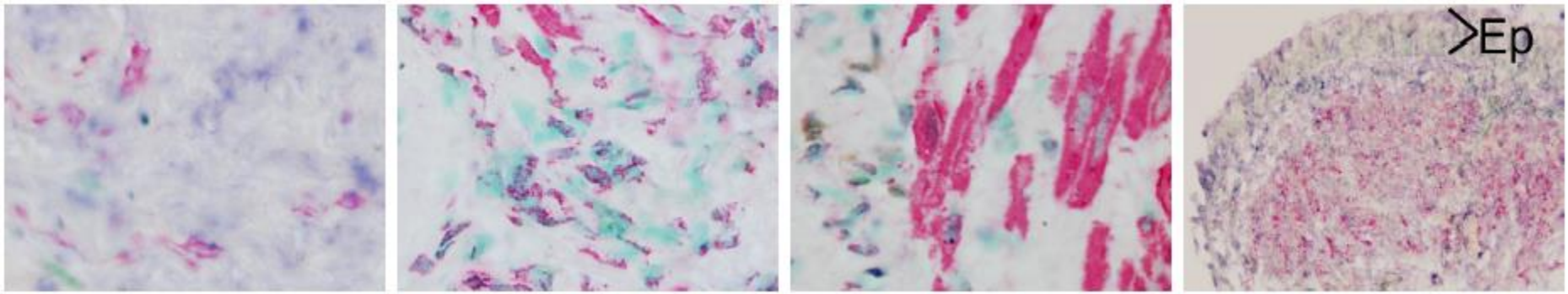
Airway smooth muscle

Control **Moderate asthma** **Severe asthma**



Non-organized airway contractile elements (NOACE)

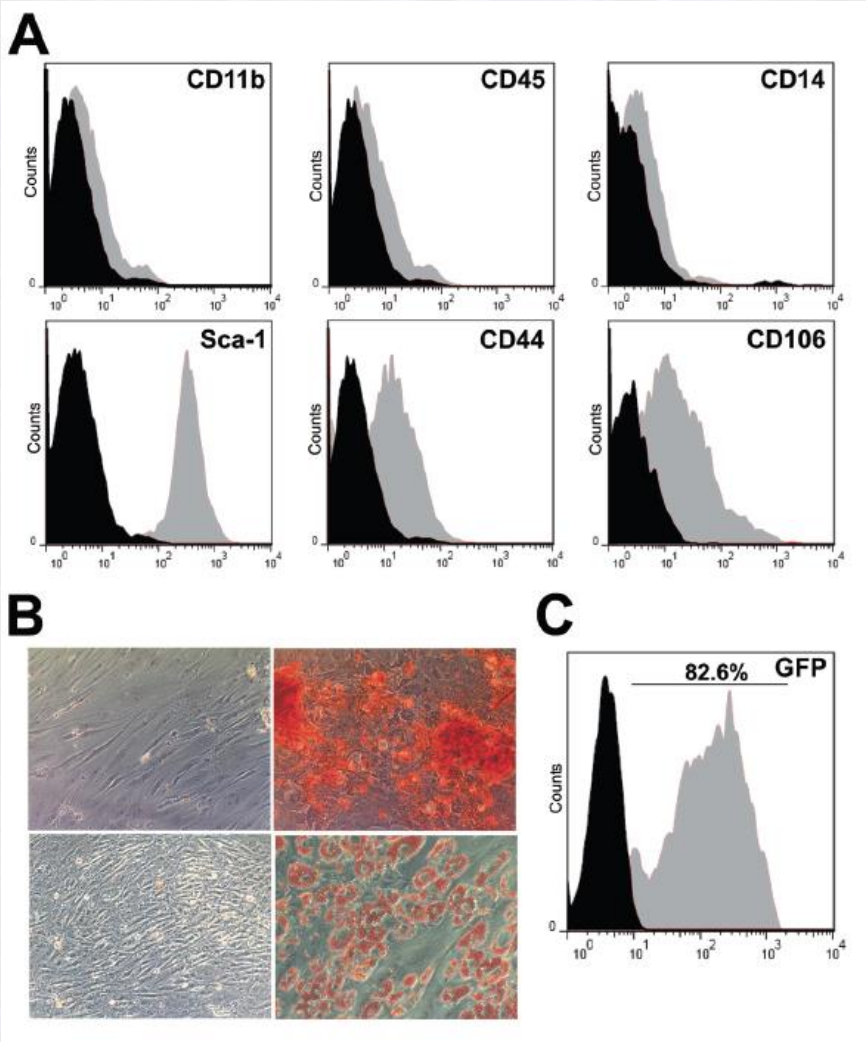
Control **Moderate asthma** **Severe asthma**

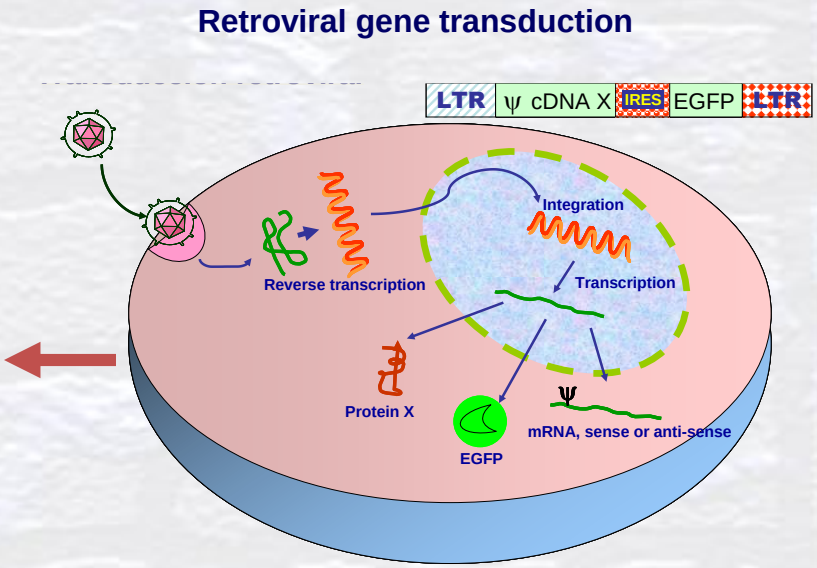


Ramos-Barbon D. *et al*. T Cells localize with proliferating smooth muscle alpha-actin+ cell compartments in asthma. *Am J Respir Crit Care Med* 2010;182(3):317-24

Hypothesis

Mesenchymal stem cells administered with a therapeutic, antiinflammatory goal for asthma may favor airway smooth muscle remodeling and thus be detrimental.



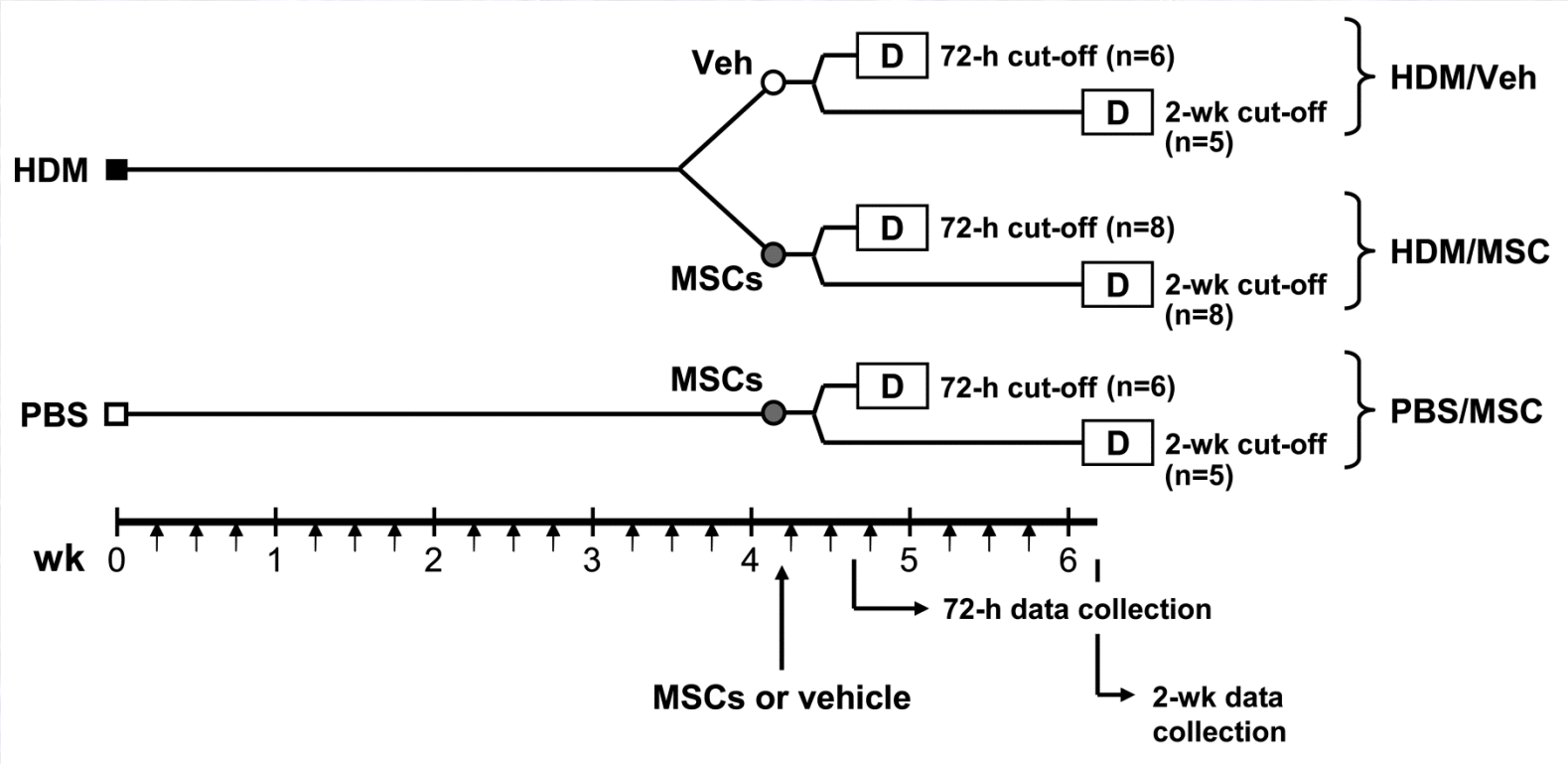


Adipose tissue mesenchymal stem cells (murine, Balb/c):

- (A) Sca-1^{+}CD44^{+}CD106^{+}CD11b^{-}CD45^{-}CD14^{-} phenotype.
- (B) Osteogenic and adipogenic differentiation.
- (C) Retroviral transduction for permanent GFP (AcGFP1 cDNA) expression.

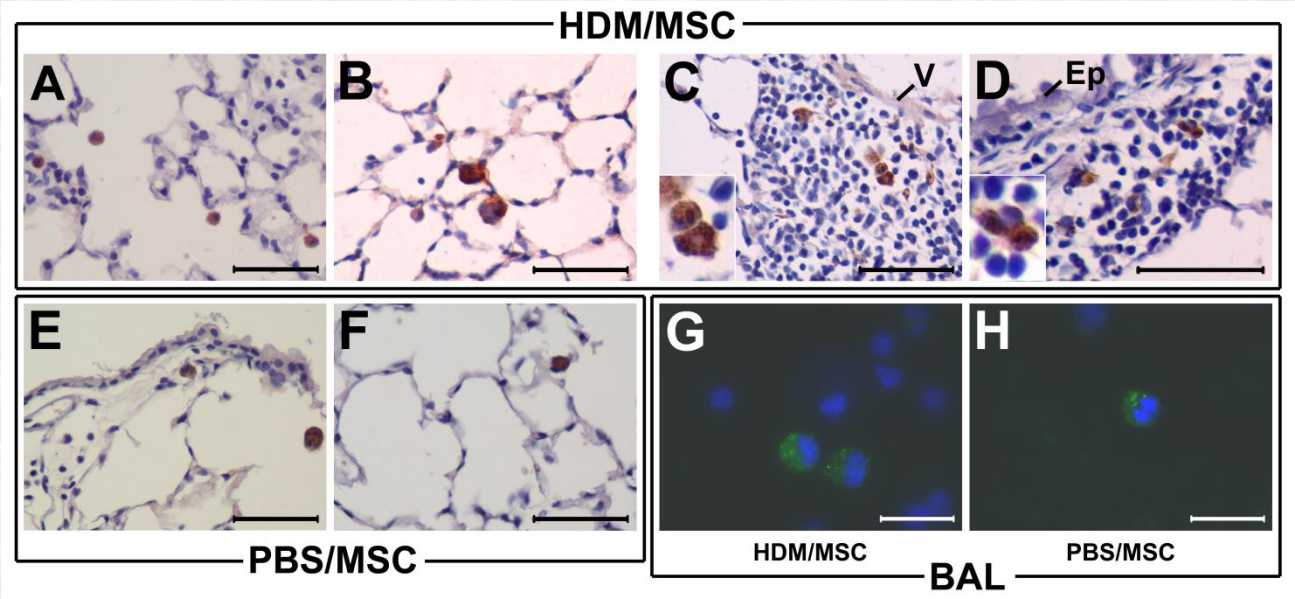
Mariñas-Pardo L et al. *Allergy* 2014;69:730-40

Study design



Mariñas-Pardo L et al. *Allergy* 2014;69:730-40

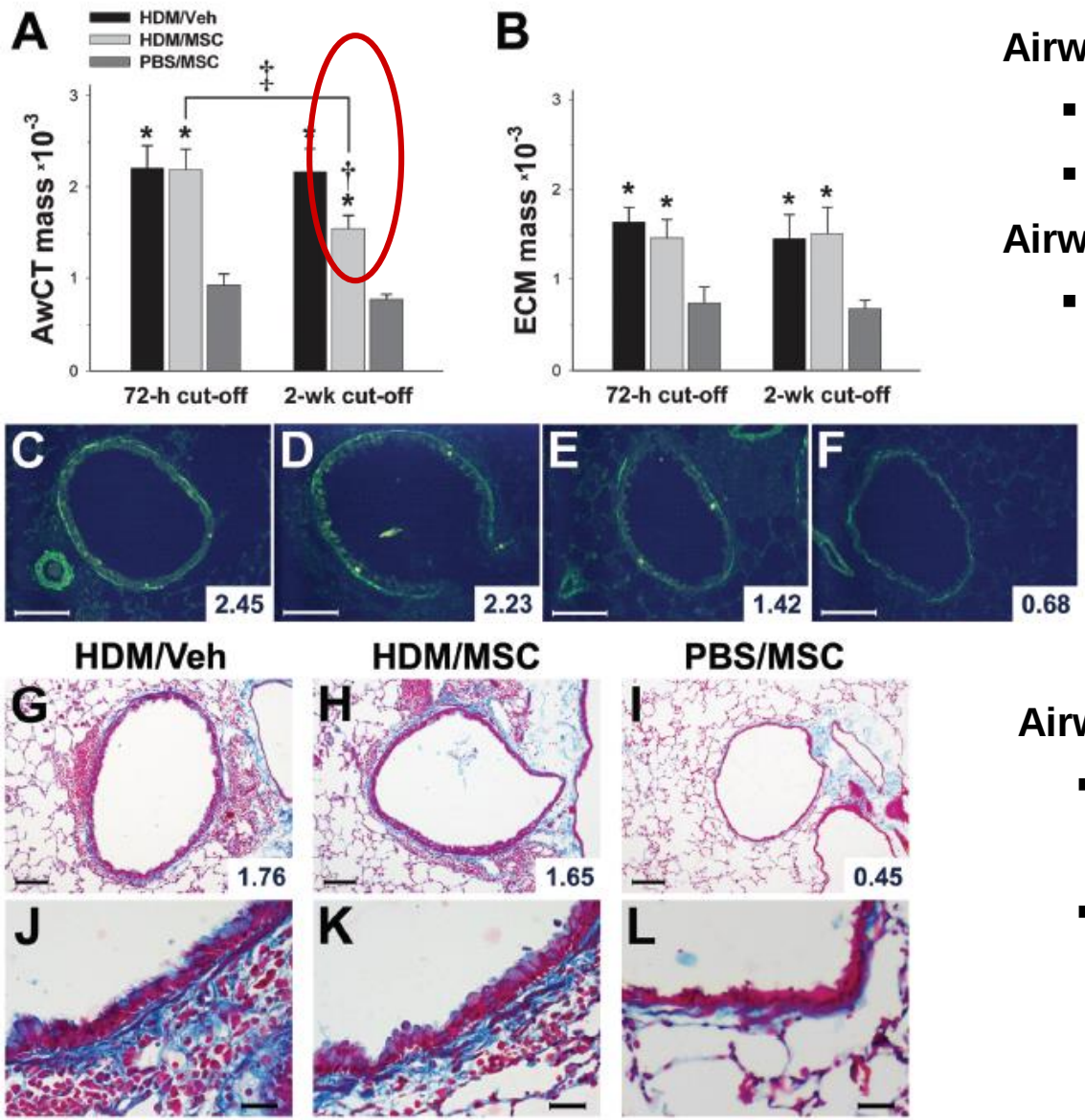
HDM: House Dust Mite extract
MSC(s): Mesenchymal Stem Cell(s)
PBS: Phosphate-Buffered Saline



GFP$^+$ cell tracking:

- Localized in air spaces, inflammatory infiltrates and BAL.
- Present at late cutoff.
- No GFP$^+$ cells integrated/differentiated in airway wall tissues.

Mariñas-Pardo L et al. *Allergy* 2014;69:730-40



Airway inflammation:

- Attenuated at early cutoff.
- Rebound at late cutoff.

Airway hyperresponsiveness:

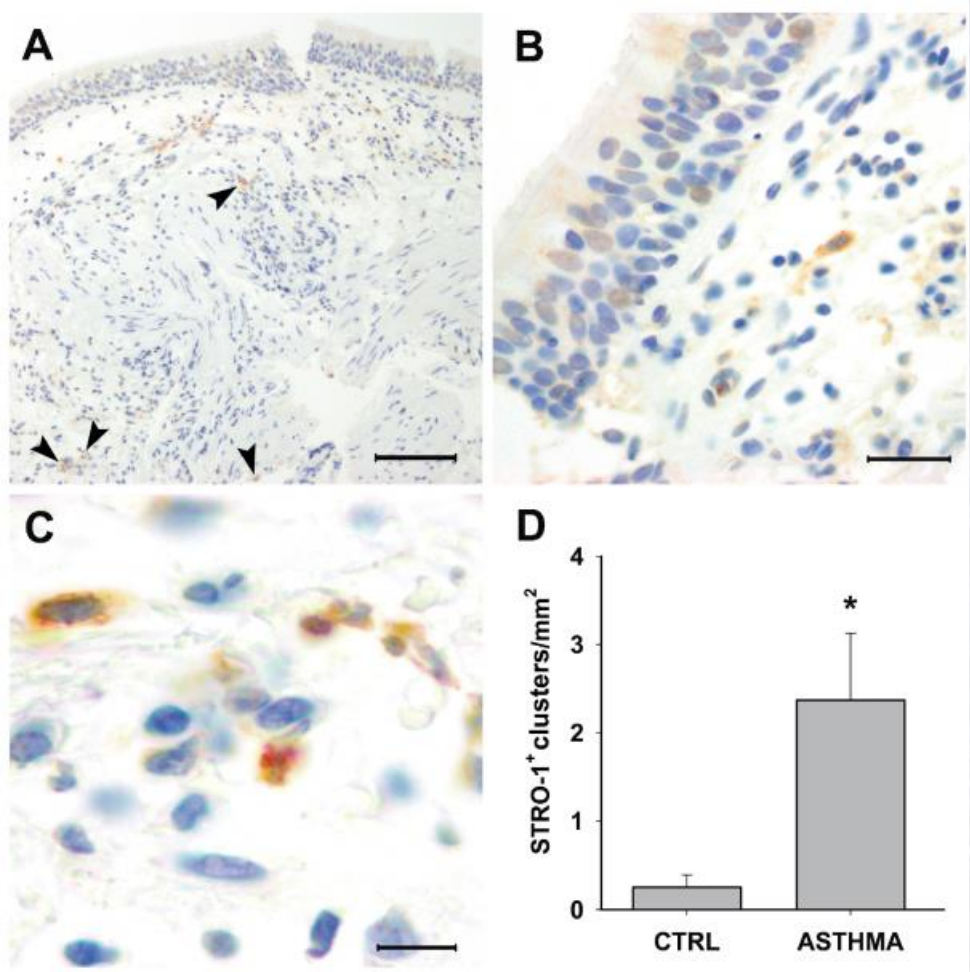
- Attenuated at late cutoff.

Airway remodeling:

- Airway contractile tissue mass decreased at late cutoff.
- Extracellular matrix unchanged.

Mariñas-Pardo L et al. *Allergy* 2014;69:730-40

Stro-1^{+} cells in bronchial biopsies



Brienza NS *et al*. Airway smooth muscle expresses mesenchymal stem cell marker Stro-1 in asthma. *Eur Respir J* 2013;42(suppl 57):172s.

Remarks

- In experimental asthma, MSCs drive a rapid decrease of airway inflammation, followed by a rebound upon continued allergen exposure. Conversely, airway hyperresponsiveness and contractile tissue mass are reduced at such late cutoff, and no MSC integration/differentiation was seen in the airway wall tissues.
- Stro-1^{+} cells are increased in bronchial biopsies of asthmatics, with Stro-1+ signal spots in the airway smooth muscle.

Acknowledgements

- **Research group:** **Óscar Amor Carro (FIS FI07/00399), Rebeca Fraga Iriso (FIS FI05/00171 & PI08/1822), Laura Núñez Naveira (FIS CD05/00250), Luis Antonio Mariñas Pardo (FIS PI05/2478), Katie White (FIS PI08/1822), Beatriz Lema Costa (INCITE07PXI916208ES), Anna Plana Bonamaisó (SEPAR), Teresa Bigorra Rodríguez, Nadia S. Brienza, Rubén Osuna Gómez, Cristina Ujaldón Navarro, Éder Fredy Mateus Medina**
- **Collaborations:** Vicente Plaza Moral, Alfons Torrego Fernández, Oriol Sibila, Diego Castillo (*Hospital de la Santa Creu i Sant Pau, Barcelona*); Santiago Bardagí Fons (*Hospital de Mataró, Mataró-Barcelona*); Carlos Martínez Rivera (*Hospital Universitario Germans Trias i Pujol, Badalona-Barcelona*); Antolín López Viña (*Hospital Universitario Puerta de Hierro, Madrid*); Francisco Javier González Barcala (*Complexo Hospitalario de Pontevedra*); Luis Pérez de Llano (*Complexo Hospitalario Xeral-Calde, Lugo*); Patrick Berger (*Université Bordeaux-2*); Javier García Castro (*Instituto de Salud Carlos III, Majadahonda-Madrid*); Xavier Muñoz Gall (*Hospital Vall d'Hebron, Barcelona*); César Picado (*Hospital Clínic, Barcelona*); Alberto Centeno Cortés, Eduardo López Peláez, Carmen Montero Martínez, Héctor Verea Hernando (*Complexo Hospitalario Universitario A Coruña*).
- **McGill University:** **James G. Martin, Qutayba A. Hamid, Elizabeth D. Fixman.**
- **Funding:** **Instituto de Salud Carlos III, Sociedad Española de Neumología y Cirugía Torácica (SEPAR), Fundació Catalana de Pneumologia (FUCAP), Xunta de Galicia; Canadian Institutes of Health Research, Canadian Lung Association, Strauss Canada Foundation; GlaxoSmithKline.**