**The Genetics of Asthma**

**Abstract**

* Positional cloning led to the ability to identify ADAM33 as an asthma susceptibility gene
* Case-Control and family based association studies = almost confirmed link between ADAM33 & asthma
* ADAM 33 expressed in mesenchymal cells
* Associated with bronchial hyperresponsiveness and accelerated lung function
  + Suggests ADAM 33’s role in airway structure (ex. Remodeling)
* Alternative splicing and tight epigenetic regulation = level of complexity in association of ADAM33 and asthma phenotype
* Role in COPD also points suggests role in airway structure (ex. Morphogenic repair)
  + ADAM33 effects are not contained to simply an asthma disease phenotype

**Intro**

* Asthma is associated with a wide range of environmental factors
* BHR (bronchial hyperresponsivness) and airway inflammation = 2 major components of asthma
* Not clear how inflammation relates to bronchial muscle hyperresponsiveness
* Third phenotype of asthma becoming increasingly recognized
  + Doesn’t respond to bronchiodialators or chorticosteroids
    - Characterized by epithelial damage and poor signaling between epithelial and underlying mesenchymal cells
      * Signaling between the two is critical for branching morphogenesis

**The Discovery of Novel Asthma Genes**

* Asthma has strong genetic components but environmental factors need to be present for these to manifest themselves
* Linkage analysis of 260 families in UK and US led to region on chromosome 20p13
  + ADAM 33 named a susceptibility gene
  + Claim made that polymorphic variation in ADAM33 could have led to 50,000 cases of asthma in the UK

**The Structure and Cellular Expression of ADAM 33**

* ADAM33 = 22 exons
  + Domains of ADAM33
    - Signal sequence
    - Prodomain
    - Catalytic domain
    - Disintegrin domain
    - C-rich domain
    - EGF domain
    - Cytoplasmic domain (long 3’ untranslated region)
* ADAM 33 mRNA is expressed in smooth muscle, fibroblasts and myofibroblasts
  + Not in inflammatory or immune cells
* Has a Ca binding site at the entrance of the active site of the catalytic domain
* Demonstrated substrates of ADAM33
  + Enzyme kinetics suggests they aren’t natural substrates
    - Stem cell factor
    - APP
    - Insulin B chain
    - TRANCE

**Alternatively Spliced Variants of ADAM33**

* Analysis of fibroblasts = at least 6 variants of ADAM33
  + None have catalytic domain
  + 2% of all mRNA transcripts have metalloprotease domain
  + selective nuclear transport is in favor of the full length molecule
  + no clear difference between biopsies in the expression of each variant between astmatic and WT

**Regulation of ADAM 33 expression**

* CpG island in ADAM33 promoter seems critical in regulation of expression
  + Island is hypermethlyated in epithelial cells but not fibroblasts
  + Demethylation of CpG islands leads to expression of ADAM33 in H292 broncial epithelial cells
    - Reinforces the importance of epigenetic regulation in the expression of ADAM33

**Association of ADAM33 with asthma subphenotypes**