**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**