Biochem – RS

The molecular basis of lung diseases

▼ Hereditary RDS (Autosomal recessive SP-B deficiency)

- SP-B from single gene in chromosome 2
- Mutation: 2 base pair insertion (codon 121)
- Causes frame-shift and premature termination
- Complete absence of proSP-B and mature
- Infants develop severe respiratory distress (like respiratory distress in premature infants but does not respond to treatment)
- Causes death if lung transplantation not performed

▼ Emphysema resulting from A1-AT (alpha 1 antitrypsin) deficiency

- Gene for A1-AT is on chromosome 14
- Single purine base mutation (GAG to AAG)
- At position 342 (positive lysine becomes negative glutamic acid)
- This mutation alters charge attraction between amino acids 342 and 290 (Fold cannot form —> tertiary structure changes —> Dimerization —> obstruction of secretion of A1-AT)
- Recessive mutation (in a heterozygote A1-AT levels are sufficient to protect alveoli)
- Can be reversed by weekly IV administration of A1-AT

▼ Emphysema from methionine oxidation

- Methionine 358 of A1-AT is necessary for binding elastase
- Cigarette smoke oxidizes Met-358
- Smoking also increases retention of neutrophils to lungs (neutrophils more attached to endothelium, and more stiff so can't escape capillary)
- Can be reversed by weekly IV administration of A1-AT

- Cystic fibrosis (thick sticky mucus builds up in lungs)
  - Autosomal recessive (Gene is on chromosome 7)
  - Defective gene codes for CFTR (that pumps CL- out)
  - Most common mutation of CFTR gene is a three-base deletion (—> loss of phenylalanine) which makes the mutant allele shorter, distinguishing it from healthy allele through PCR and gel electrophoresis (mutant allele moves further and faster)
  - Defected CFTR causes CL- ions to remain in cells, which takes up water from surrounding (osmosis) making mucus thick in several organs
  - Thick mucus favors infections like pneumonia, so if left untreated children rarely survive more than 5 years
  - Has no cure (but treatments that prevent and control infection as well as loosen and remove mucus are improving)

▼ Immobile cilia syndrome (primary ciliary dyskinesia)

- Rare autosomal recessive
- Abnormalities in ciliary structure and function (later found that it is caused by disorganized motion —> uncoordinated and ineffective clearance)
- Leads to respiratory secretions to collect, thicken and promote infection
- Permanent lung damage develops at an early age without treatment (which may make patients need lung transplantation)
- Goal of treatment: Minimize damage caused by chronic infection (airway clearance therapy, secretion removal and bronchodilation, and aggressive antibiotics

▼ Possible defects in cilia

1) Dynein arm: Outer and inner are totally or partially absent, OR only outer Or only inner OR short dynein arms

2) Radial spoke: total absence of radial spoke OR Absence of head

3) Microtubular transposition: Absence of central tubules AND Outer doublet go to the center

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