Familial Hypercholesterolemia

Erik Wong #11- Human Genetics, Period 6

Symptoms

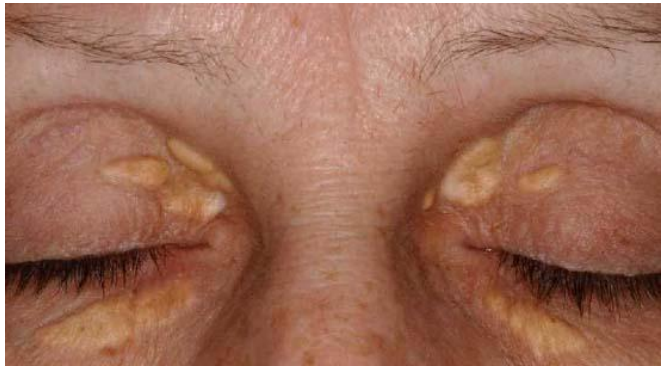

Fig 1

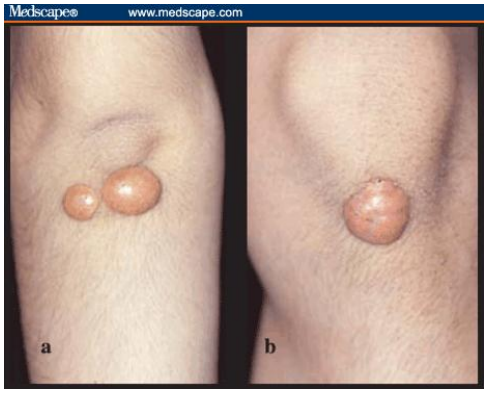

Fig 2

- -early onset
- -autosomal dominant (talk a a bit later)
- BUILDUP of LDL (low-density lipoprotein)
- Xanthemas-LDL buildup, fatty deposits around hand, elbows, knees, etc.
- Xanthelasmas- fatty deposits on eyelids
- Cardiovascular disease- atherosclerosis, angina, high blood pressure, heart attack

Molecular Cause

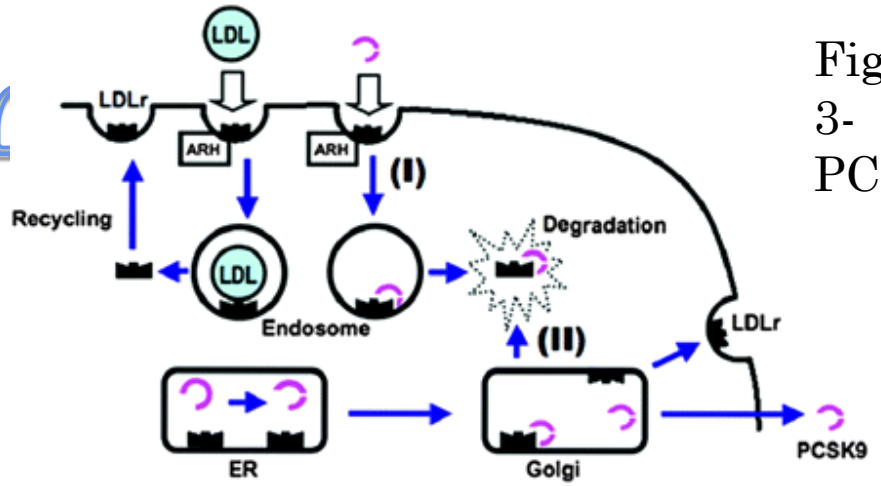

Figure 3- PCSK9

- **LDL receptor** on chromosome 19, 919013.1-13.3 (mostly) (**autosomal dom**)

-heterozygotes have LDLR activity of 2-25%, homozygotes have less than 2%

-5 classes 1) receptor not synthesized 2) LDLR does not move from ER to Golgi 3) LDLR cannot bind to LDL 4) binding successful but no cluster for endocytosis 5) receptor does not recycle back to cell surface

-**Apiloproprotein (ApoB)-** second chromosome (2024-p23). Arginine is replaced with glutamine at position 3500, resulting in the mutation of 3500Q. The section of LDL that binds with the receptor undergoes mutation the prevents the binding from initiating.

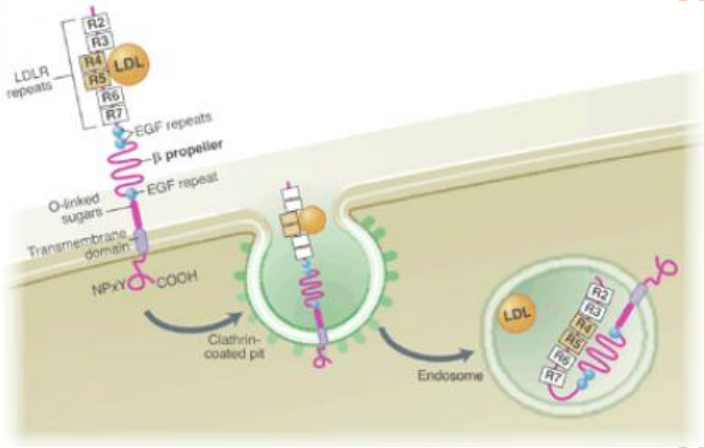

Fig 4- LDLR cause

-**Proprotein convertase subtilisin/kexin type 9 (PCSK9)-** binds to epidermal growth factor-like repeat A (EGF-A) domain of the LDLR, thus cointernalizing it, and inducing LDLR degradation in the lysosome

-low density lopoprotein receptor adapter protein 1 (LDLRAP1)- autosomal recessive- LDLR cannot transport into liver cells, so LDL is still in the bloodstream

Cures/treaments

- -diagnose through ultrasound (echocardiography see image of heart), family trees (determine if caused by ApoB or not), cardiac MRI (magnetic resonance imaging),
- Apheresis-regulated blood/plasma in an out of body by centrifugation, and filter out LDL
- Change your lifestyle-less saturated fat (red meats), low-fat dairy products, more exercise
- Statins(92% of drugs bought in 2001-inhibit HMG-CoA reducatase, very important in the production of cholesterol in the liver (eg Simvastatin (43%) and atorvastatin (32%) or drugs bought in 2004.

Fig 5

Proposed cure/limits

- Patient must first be diagnosed with PCSK9 as cause by study of hepatocytes
- -block intracellular pathways between PCSK9 and LDLR with cysteine proteases
- can cause cleavage of PCSkK9's peptide bonds by pairing the eponymous residue with a proton-withdrawing group to promote nucleophilic attack (attacking the H^+ ion). As result, the PCSK9 will not mature in the cell, and the LDLR would not be not be degraded in the lysosome.
- Problems-antibody could also work against PCSK9, cysteine proteases may affect other proteins in the cell by accident

References

- Fig 1- akronics.com
- Fig 2- medscape.com
- Fig 3- http://atvb.ahajournals.org/content/30/7/1279/F1.expansion.html
- Fig 4- http://rivedalgen677s10.weebly.com/domains-protein.html
- Fig 5-http://www.simvastatin-sideeffects.org/