Duchenne Muscular Dystrophy (DMD)

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Physiology

- Most common muscular dystrophy: 1:4000 incidence (mostly boys)
- Some clinical variability, muscular system disorder.
- Muscular system target: muscle cells eventually die from intracellular leakage and attacks from cytotoxic T cells
- Average IQ of 85; gait abnormality; Gower sign
- Three major milestones: when DMD-affected patients begin to walk, when they lose their ability to ambulate, and when they die; death usually occurs by 3rd decade of life (respiratory infection → cardiopulmonary compromise)
**Molecular Cause**

- Transmission: X-Linked Recessive; spontaneous mutation occurs in about 1/3 of cases
- Most common mutations are on short arm of X chromosome, location Xp21; mutations prevent dystrophin, a component of the cytoskeleton of the cell membrane, from being coded
- Interferes with translation reading frame or promoter sequence; synthesizes unstable, ineffective protein
- Dystrophin accounts for about 0.002% of proteins in striated muscle; it acts as a homotetramer at the costameres in skeletal muscles, as well as associates with actin at its N-terminus and the DAG complex at the C-terminus, forming a stable complex that interacts with laminin in the extracellular matrix
- A lack of dystrophin will lead to leakage of intracellular materials; this results in high levels of creatine phosphokinase (CPK); less active forms may still function as a sarcolemmal anchor; macrophages invade in the end anyway; dead muscle are replaced by fibrofatty infiltrate
Treatments /
Risks and Limits

- DMD has no cure; treatment is focused on delaying onset of symptoms and improving standard of life

- Steroids (deflazacort) can be beneficial but have limited effect

- Palliative care: physical therapy includes splints, wheelchairs, minor exercise, and occupational therapists

- Surgery can be used to treat scoliosis and contractures; progressive when patient is non-ambulatory

- Novel methods: somatic gene therapy, PTC124, viral vectors, and antisense oligonucleotides (AONs)

- Gene therapy: healthy immature myoblasts introduced into diseased muscles; fuse and stimulate dystrophin; MDX model has shown more dystrophin but no improvement

- Viral vectors: Biostrophin uses ‘micro-dystrophin,’ or a small copy of the dystrophin gene; lacks functional regions (little clinical improvement)

- AONs: PRO051/51 and AVI-4658 focus on skipping exon 51; technique could be applied to other exons (phase 2)

- Ataluren; molecule PTC124 bind to ribosomes, overrides nonsense stop translation signals ‘UGA’ (phase 2)
Proposed Cure/ Limits

- MDX mice model is the widely used model; a common single base substitution within exon 23 → premature stop codon; relatively mild compared to humans; up-regulation of utrophin; can also have a splice site in 43, mutation in 53, etc.

- Proposal is to improve PRO051/GSK; use multiple AONs and Ataluren

- We use DNA oligos to bind to RNA to form hybrids which activate RNase; enzyme cleaves the double-stranded mRNA, preventing the translation into protein; strategy is mutation specific, uses hotspots (exons 43-53, minor exons 2-20)

- We also use PTC124 is an orally taken, small molecule drug; it is meant to induce dose-dependent read-through of all nonsense codons UAA, UAG, or UGA in mRNA coding region

- Reverse-transcriptase-polymerase-chain-reaction to analyze the transcript region flanking the mutations

- MDX model limited by specific mutations; independent variables difficult to track, PTC124 operates as a relatively unknown (unique) molecule; submit successful standard 6-minute walk tests in humans (phase 1) to higher phases
References

Text


Images

- http://en.wikipedia.org/wiki/Duchenne_muscular_dystrophy (Fig.1)
- http://www.humanillnesses.com/original/Men-Os/Muscular-Dystrophy.html (Fig 2.)
- http://cdn.intechopen.com/pdfs/38140/InTech-Aon-mediated_exon_skipping_for_duchenne_muscular_dystrophy.pdf (Fig. 3-5)