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HST.161 Molecular Biology and Genetics in Modern Medicine
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Lecture 3

Muscular Dystrophies

Example of paper presentation for discussion sections, on the taste receptor papers assigned for today:

Adler, Elliot, Mark A. Hoon, Ken L. Mueller, Jayaram Chandrashekar, Nicholas J. P. Ryba, and Charles S. Zuker. "A Novel Family of Mammalian Taste Receptors." *Cell* 100 (2000): 693-702.

Chandrashekar, Jayaram, Ken L. Mueller, Mark A. Hoon, Elliot Adler, Luxin Feng, Wei Guo, Charles S. Zuker, and Nicholas J. P. Ryba. "T2Rs Function as Bitter Taste Receptors." *Cell* 100 (2000): 703-711.

Begin presentation with some background information that may not present in the paper. (For example, a map of the areas of particular taste receptors on the tongue, explanation of why the bitter taste receptor has been developed, overview of papillae, G-protein-coupled receptors, etc.)

Bitter taste sense was developed to protect against eating things that might be spoiled, poisonous, etc.

Each cell has a few different types of receptors on it, but they all taste the same thing (so, multiple different types of bitter receptors). Each taste bud has different types of cells, which can sense different tastes. There are areas of taste buds with higher concentrations of cells that sense particular tastes.

Gustducin: a tongue-specific G-protein.

Then, move into the actual information from the paper. Begin by identifying the questions the authors sought to answer. The authors of these papers were interested in studying gustation: what are the receptors for different tastes? How are these receptors organized into a sensory system?

Then describe how they proceeded and what, if any, answers they found: Genetic linkage studies identified a particular locus for the ability to respond to a particular (bitter) taste. Identified a new family of receptors, and looked at sequence conservation across different members of the family, across different species (mouse, human, rat).

- What evolutionary relationships exist?

Looked at concentration of the protein on the tongue. Any bitter taste cell was found to have more than one type of bitter taste receptor.

Second paper:

This presentation focuses on the three most critical figures/pieces of data.

The first paper identified taste receptors and where they're located.
This paper confirms whether certain proteins actually function like taste receptors.

The first figure demonstrates a successful method for detecting intracellular Ca^{2+} when a cell/receptor is activated with its agonist (so in practice, it also detects when a signal cascade occurs via a G-protein-coupled receptor).

The next figure looks at some of the taste receptors identified in the first paper and uses the Ca^{2+} detection method on these cells, after adding their agonists. These proteins do, in fact, look like functional receptors due to spikes in Ca^{2+} .

Third figure is further characterization of the receptors. Added cyclohexamide (bitter compound) once; saw very strong peak in intracellular Ca^{2+} ; desensitization was observed after repeated exposure. Added a number of other compounds; only saw a response with cyclohexamide, the bitter taste.

Brief introduction to LOD Scores

LOD scores measure the amount of linkage between two genes.

Linkage tests begin with a situation like this: [see paper sheet]

Model 1: Always linkage between two genes at some distance, conventionally named theta, where $\theta = 0$ to 0.5

Model 2: No linkage.

The Muscular Dystrophies: An Introduction

By Dr. Brown

A. Muscle in general:

Muscle is developed by fusion of myoblasts, which create myotubes, which are integrated to form normal muscle. Cells are polygonal, tightly packed together, eccentrically positioned nuclei (on the cells' periphery). Normal muscle is able to regenerate by recruiting stem-like cells.

B. Overview of muscular dystrophies:

1. Duchenne: X-linked recessive (so it tends to affect boys). At birth, a boy looks normal, but is slow to develop motor milestones and he's never able to run normally or stand up from sitting without trouble; after a few years of age, he develops a distinctive body curvature. Disease worsens severely over the first decade of life; legs are usually completely paralyzed by 12-13 years old. By late teens, almost all skeletal muscles are paralyzed. May develop secondary symptoms like scoliosis. Ultimately ends in early death.

2. Becker Muscular Dystrophy: “diluted” Duchenne; reduced, develops later (in adulthood).

Dystrophin (protein)

In Duchenne, you see aggressive cell degeneration and scarring in between cells. Absent or diminished amounts of dystrophin; in Becker, it may be truncated but it functions at least partially like normal. Collagen deposition is prominent in late-stage muscular dystrophy. Window of therapeutic intervention closes at some point, because cells become encased in scar tissue.

GRND dogs not only exhibit problems in their skeletal muscle but also in cardiac muscle.

3. Autosomal recessive disorder related to Duchenne (LGMD – limb girdle muscular dystrophy); weakness begins around age 5-10 y.o., ultimately results in being confined to a wheelchair. Involves a different protein, dystroglycan.

4. Some forms of congenital muscular dystrophy are related to LGMD and Duchenne. One recessively inherited form is caused by skeletal muscle merosin; babies are born already deformed and weak. (Merosin deficiency also causes defects in the brain).

5. The last type begins much later in life, proximal weakness and scarring; dominant inheritance; involves collagen genes.

6. Calcium-dependent protease implicated in a type that onsets in childhood/adolescence.

c. Disorders of membrane organization and repair: Miyoshi muscular dystrophy and LGMD-2B; Caveolinopathies

Miyoshi Myopathy:

- onset: late teens, early 20s
- initial weakness in gastrocnemii
- extremely high serum CPK
- relentless but slow progression
- dysferlin protein (fer-1 homologue) implicated in this and LGMD-2B
- normal dysferlin function is relevant to normal muscle healing after exercise

C. Comments on Therapy

Conventionally, by defining individual components of the disease, you identify targets for therapy; when just treating these elements you might delay it, or make it more mild, but you don't prevent or cure the whole disease;

New approaches to therapy for dystrophin deficiency:

- Replacement:
 - o Systemic delivery of dystrophin gene (viral; hard to package, hard to deliver)
 - o Exon skipping (bypass mutant stop codons to produce functional exons by binding specifically to these codons and excising them)
 - o Naked cDNA therapy
 - o Cell therapyNone of these are ready for human trials.

- Compensation:
 - o Up-regulation of related genes
 - o Enhancement of muscle bulk

Determinants of muscle bulk:

- innervation
- exercise
- nutrition
- hormonal/molecular factors
- metabolic status
- genetic variables

Myostatin is a suppressor of muscle growth; inactivation causes muscle hypertrophy. Mutations (myostatin inactivations) have been observed in cattle and humans; both can generally survive and are healthy.