UNDERSTANDING KENNEDY’S DISEASE

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NIH definition

...progressive neurological disorders that destroy motor neurons, the cells that control essential voluntary muscle activity such as speaking, walking, breathing, and swallowing...When there are disruptions in the signals between the lowest motor neurons and the muscle, the muscles do not work properly; the muscles gradually weaken and may begin wasting away and develop uncontrollable twitching (called fasciculations).


IN THE EYES OF NIH...

KENNEDY’S DISEASE IS A MOTONEURON DISEASE
WORKING ASSUMPTIONS

• Motoneuron death accounts for the progressive loss of motor function in motoneuron disease

• Because motoneurons die, it must be that the toxic agent acts directly in motoneurons to cause their death

• Muscle wasting in motoneuron disease accounts for the loss of muscle strength

• Loss of muscle strength is a secondary event caused by a loss of synaptic connections from motoneurons to muscle fibers
WHAT IS MY GOAL?

I want to...
UNDERSTAND WHY MOTOR FUNCTION DETERIORATES

WHAT ARE THE EVENTS THAT TRIGGERS MOTOR DYSFUNCTION EARLY ON
WHAT ARE THE EVENTS BEHIND THE PROGRESSIVE WORSENING OF MOTOR DYSFUNCTION OVER TIME
MY APPROACH?

- I am opportunistic…I study different mouse models of KD developed by different investigators

3 main models:
- KI
- 97Q
- Myo

2 new models:
- Myo_{mutant}
- Mot_{mutant}

Lieberman
Sobue
Jordan
Monks
WORKING ASSUMPTION #1
MOTONEURON DEATH ACCOUNTS FOR THE PROGRESSIVE LOSS OF MOTOR FUNCTION IN MOTONEURON DISEASE
ALL 3 MODELS SHOW PROFOUND LOSSES IN MOTOR FUNCTION WITHOUT MOTONEURON LOSS

Knock-in model

Impact of motoneuronal retrograde transport in two models of SBMA implicates two sites of androgen action

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- Figure showing motoneuron number and soma area comparison between WT and KI males in the hang test.
All 3 models show profound losses in motor function without motoneuron loss.

Testosterone Reduction Prevents Phenotypic Expression in a Transgenic Mouse Model of Spinal and Bulbar Muscular Atrophy

Masahisa Katsumo,1,4 Hiroaki Adachi,1,4 Akito Kume,1 Mei Li,1 Yuji Nakagomi,2 Hisayoshi Nawa,1,3 Chen Sang,1 Yasushi Kobayashi,1 Manabu Dojo,1 and Daisuke Obata3,5

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spinoocerebellar ataxia, and other polyglutamine diseases such as Huntington's disease (Zoghbi et al., 1992), spinocerebellar ataxia (Zoghbi and Orr, 2000), and selective involvement despite widespread expression of the disease gene (Zoghbi and Orr, 1999), and selective involvement despite widespread expression of the disease gene (Zoghbi and Orr, 1999) as well as other polyglutamine diseases (Davies et al., 1999; Zoghbi and Orr, 2000).

Previously, we reported reduced gonadotropin levels at the protein level (Kume et al., 1999; Zoghbi and Orr, 2000).
ALL 3 MODELS SHOW PROFOUND LOSSES IN MOTOR FUNCTION WITHOUT MOTONEURON LOSS

Overexpression of wild-type androgen receptor in muscle recapitulates polyglutamine disease

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Graphs showing:
- **HANG TIME (SEC)**: Line 78 vs. Line 141
- **Motoneuron number**: WT vs. myo
- **Mean soma area (μm²)**: WT vs. myo
CONCLUSION?

MOTONEURON DEATH *PER SE* DOES NOT CAUSE THE LOSS IN MOTOR FUNCTION

even though it may contribute to the worsening symptoms over time
WORKING ASSUMPTION #2
WHEN MOTONEURONS DIE, IT MUST BE THAT THE TOXIC AGENT ACTS DIRECTLY IN MOTONEURONS TO CAUSE THEIR DYSFUNCTION AND DEATH
SO...
WHILE WE THINK MOTONEURON DEATH DOES NOT TRIGGER (AND MAY NOT UNDERLIE) MOTOR DYSFUNCTION...

WE CAN STILL ASK...

DO MUTANT ANDROGEN RECEPTORS ACT IN MOTONEURONS TO CAUSE THE LOSS OF MOTOR FUNCTION?
WELL...APPARENTLY NOT
Muscle Expression of Mutant Androgen Receptor Accounts for Systemic and Motor Neuron Disease Phenotypes in Spinal and Bulbar Muscular Atrophy

Constanza J. Cortes,1 Shuo-Chian Ling,2,11 Ling T. Guo,3 Gene Hung,4 Taiji Tsunemi,3,12 Linda Ly,1 Seiya Tokunaga,2 Edith Lopez,1 Bryce L. Sopher,5 C. Frank Bennett,2 G. Diane Shelton,5 Don W. Cleveland,2,12 and Albert R. La Spada1,4,6,7,9,10,*

Peripheral Androgen Receptor Gene Suppression Rescues Disease in Mouse Models of Spinal and Bulbar Muscular Atrophy

Andrew P. Lieberman,1,* Zhigang Yu,1 Sue Murray,2 Raechel Peraita,2 Audrey Low,2 Shuling Guo,2 Xing Xian Yu,2 Constanza J. Cortes,3 C. Frank Bennett,2 Brett P. Monia,2 Albert R. La Spada,3,4,12 and Gene Hung2,*
CONCLUSION?

NOT ONLY DOES MOTONEURON DEATH NOT ACCOUNT FOR THE LOSS IN MOTOR FUNCTION
BUT
THE MUTANT ANDROGEN RECEPTOR DOES NOT APPEAR TO ACT IN MOTONEURONS TO CAUSE MOTOR DYSFUNCTION
WORKING ASSUMPTION #3

MUSCLE WASTING IN MOTONEURON DISEASE ACCOUNTS FOR THE LOSS OF MUSCLE STRENGTH
Contractile dysfunction in muscle may underlie androgen-dependent motor dysfunction in spinal bulbar muscular atrophy
Kentaro Oki, Katherine Halievski, Laura Vicente, Youfen Xu, Donald Zeolla, Jessica Poort, Masahisa Katsuno, Hiroaki Adachi, Gen Sobue, Robert W. Wiseman, S. Marc Breedlove and Cynthia L. Jordan
LOSS OF MUSCLE CONTRACTILE FORCE OCCURS INDEPENDENT OF MASS
MUSCLE WASTING DOES NOT EXPLAIN THE LOSS OF MUSCLE STRENGTH
(even though wasting can and may contribute significantly to lost muscle strength in the later stages)
WORKING ASSUMPTION #4
LOSS OF MUSCLE STRENGTH IS A SECONDARY EVENT CAUSED BY DENERVATION OF MUSCLE FIBERS

Muscle denervation = loss of synaptic inputs
Neuromuscular junctions are pathological but not denervated in two mouse models of spinal bulbar muscular atrophy

Jessica E. Poort¹, Mary B. Rheuben¹, S. Marc Breedlove¹ and Cynthia L. Jordan¹,*
NEUROMUSCULAR JUNCTIONS ARE NOT DENERVATED IN DISEASED KI OR MYO MICE
NEUROMUSCULAR JUNCTIONS ARE NOT DENERVATED IN DISEASED 97Q MICE
MUSCLE DENERVATION DOES NOT EXPLAIN THE LOSS IN MUSCLE STRENGTH AND MASS
(even though denervation may contribute to the worsening of symptoms as the disease progresses)
ARE THERE DEFECTS IN SYNAPTIC FUNCTION THAT COULD EXPLAIN THE LOSS OF MOTOR FUNCTION?

Neurobiology of Disease

Defects in Neuromuscular Transmission May Underlie Motor Dysfunction in Spinal and Bulbar Muscular Atrophy

Yufen Xu, Katherine Halievski, Casey Henley, William D. Atchison, Masahisa Katsuno, Hiroaki Adachi, Gen Sobue, S. Marc Breedlove, and Cynthia L. Jordan

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YES, THERE ARE DEFECTS IN SYNAPTIC FUNCTION

Weaker synapses in motor-impaired mice:
They release less excitatory juice (acetylcholine) to stimulate muscle contraction
A LOSS OF MOTOR FUNCTION IS LIKELY DUE TO:

1. Primary defects in muscle function
2. Secondary defects in synaptic function
WHAT IS BEHIND THE DISCREPANCY?
MODELS VS PATIENTS
NEXT TALK...

THEME: NOT ALL MUSCLES ARE CREATED EQUALLY

BDNF helps some muscles but not others
ACKNOWLEDGEMENTS

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Ashley Monks
Jamie Johansen

Weak muscles
Ken OKi

Deficit in muscle BDNF mRNA
Kathy Halievski

Disrupted NMJs
Jessica Poort

Weak synapses
Youfen Xu

Impaired retrograde transport
Mike Kemp

AR (working in muscle)
THANK YOU!