A Consensus Model for FSHD Identifies Opportunities for Therapy

Stephen J. Tapscott, MD, PhD
Fred Hutchinson Cancer Research Center
Seattle, WA
Light = Genes On
Euchromatin

Dark = Genes Off
Heterochromatin
Light = Genes On
Out in the living room

Dark = Genes Off
Stored in the attic
Stem Cell Genes
- On, Living Room

Stem Cell Genes
- Off, Attic
Stem Cell Genes - On, Living Room

DNA Methylation & Heterochromatin
Lock the Attic Door

Stem Cell Genes - Off, Attic

Stem Cell

Differentiated Cell
DUX4 is abundantly expressed in healthy human testis

Snider, Geng et al. PLoS Genet, 2010

Brown = DUX4 immunodection
Fewer D4Z4 repeats have less repressive heterochromatin

11-100 D4Z4 repeat units: heterochromatin

1-10 D4Z4 repeat units: less heterochromatic

= heterochromatin (H3K9me3, H3K27me3, meCpG)

= less heterochromatic (H3K4me3, less meCpG)
Variegated endogenous DUX4 expression in FSHD muscle cells
A Developmental Model of FSHD

• DUX4 is expressed in the testis germ-line
  – Possible role in stem cell biology
• DUX4 is repressed (moved to the attic) in muscle
  – Repeat-mediated silencing
• Inefficient repression causes FSHD
  – Fewer repeats = less efficient repression
  – Faulty lock (e.g., SMCHD1 in FSHD2)
• Results in occasional bursts of DUX4 in muscle
**DUX4 is a transcription factor**

- **DUX4 can “turn-on” other genes**
  - When DUX4 comes out of the attic it brings a lot of genes with it!

- **Turns on germline genes in skeletal muscle**
  - Tells the muscle to become a germline cell
Candidate Mechanisms for FSHD

• Activation of a germline program muscle cells
  – Confusion causes death and dysfunction

• Immune response to germline proteins
  – FSHD cells express Cancer Testis Antigens
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- And more ….
Therapeutic Opportunities

• Suppress DUX4 mRNA expression
  – General enhancement of chromatin repression
  – Targeted enhancement of D4Z4 chromatin repression
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• Interfere with pathological mechanism(s)
  – Multiple candidate mechanisms downstream of DUX4
  – Which one(s) contribute most to disease?
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Preclinical Models

• Cultured FSHD muscle cells
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Variegated endogenous DUX4 expression in FSHD muscle cells

Snider et al, PLoS Genet 2010; Geng et al, Dev Cell 2012
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- Mouse with human DUX4 genomic region

Krom et al, PLoS Genet 2013
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- Human-to-mouse muscle transplants

Parker et al Skeletal Muscle 2012
Parker et al Stem Cells 2012
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Snider et al, Hum Molec Genet 2009
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- Model organisms
Identifying Candidate Therapies

• Screen existing chemical compounds
  – FDA approved compounds
  – Clinical candidate compounds
  – Screen large chemical libraries
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• Lifestyle, diet, exercise
Milestones for Success

• Halt or reverse disease progression
  – Slowly progressive disease
    • Requires long-term study
    • Large numbers of participants
  – Natural history studies and FSHD registries
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  – MRI or serum markers of muscle damage
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Small numbers of participants
Short-term studies

Prioritize candidate therapies
Milestones for Success

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Large numbers of participants
Long-term studies

Outcome studies for FDA approval
How long will it take?

• Within a few years if ... ?
  – FDA approved drug
  – Repurposed drug candidate
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• Within a decade if ... ?
  – New drug development
  – Progressively more effective drugs
When will we start?

• We have, thanks to you!
  – Consensus model of disease
  – Candidate biomarkers
  – Clinical natural history studies
  – Multiple efforts at drug development

Tawil et al, Skeletal Muscle 2014
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