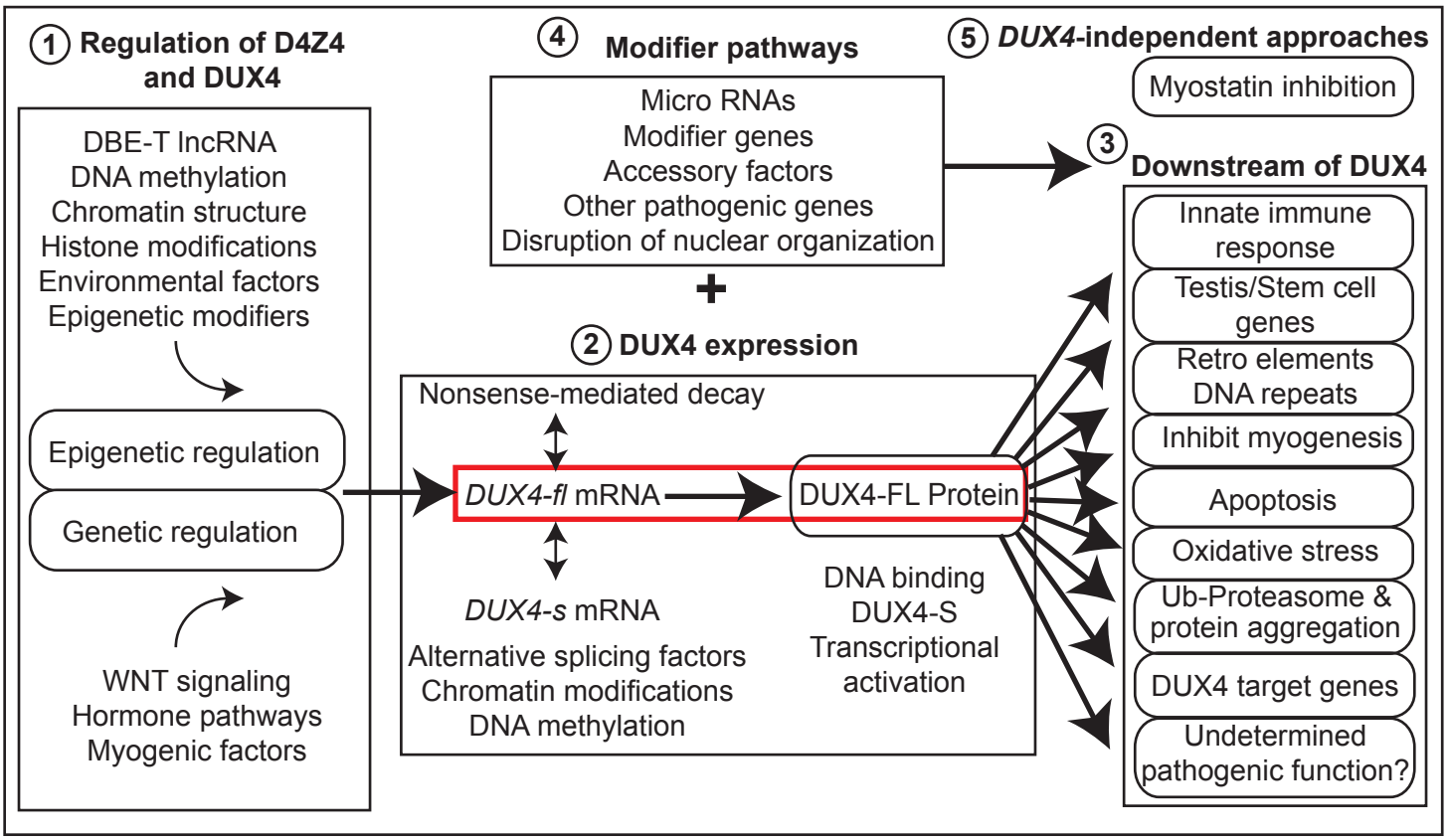
FSHD Therapeutic Approaches: Overview

FSHD is a pathogenic gain-of-function disease.

Most other muscular dystrophies result from mutations resulting in loss-of-function effects in muscle structural proteins, gene regulation pathways, or cell signaling pathways. Thus, these need to be "fixed" or replaced.

FSHD is conceptually different from a therapeutic perspective.

In FSHD, the DUX4 protein needs to be removed or destroyed, or its pathogenic activity blocked.
Thus, FSHD is amenable to numerous therapeutic technologies.

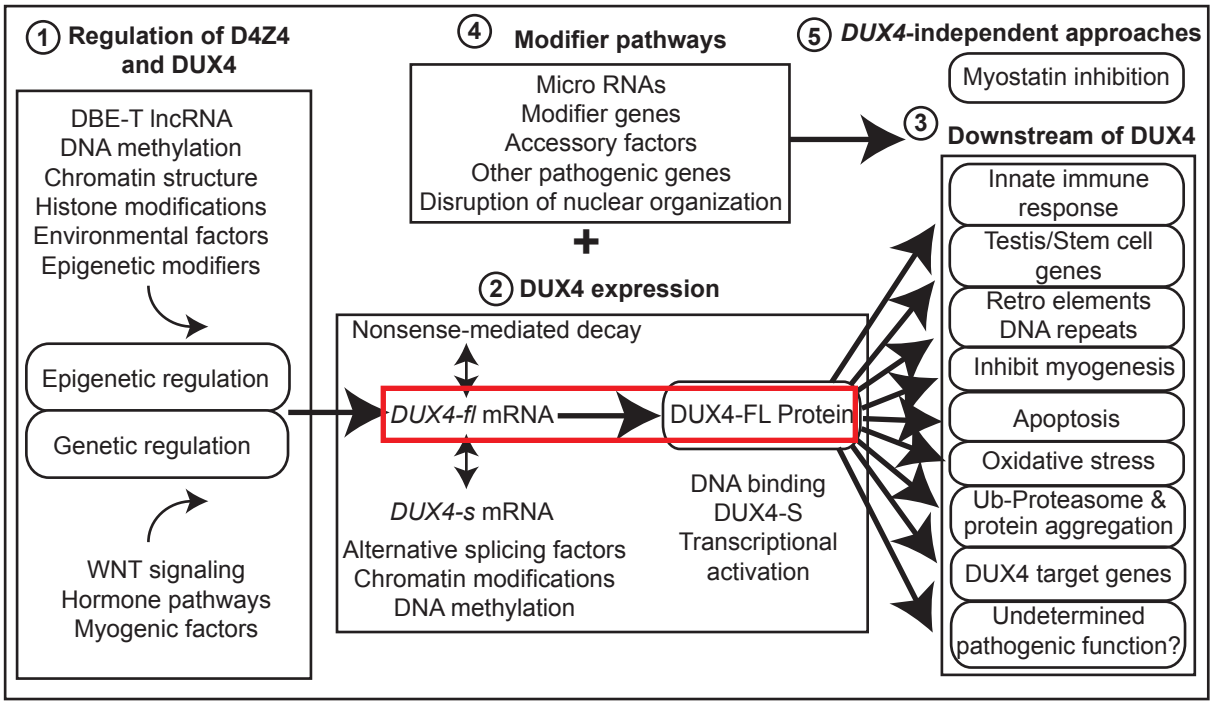


FSHD therapeutic targets include the regulation of 1) *DUX4* gene expression, 2) the DUX4 mRNA and protein, 3) DUX4-FL downstream pathways, 4) *DUX4* modifier genes and factors, and 5) *DUX4*-independent pathways.

FSHD Therapeutic Approaches: Overview

FSHD is a pathogenic gain-of-function disease.

In FSHD, *DUX4* expression needs to be repressed, or its mRNA/protein destroyed, or its downstream pathogenic activities blocked.



FSHD therapeutic targets:

1) Regulation of *DUX4* gene expression
   small molecule transcriptional inhibitors; CRISPR inhibition; CRISPR/Cas9 DNA editing; CRISPR/Cas base editing; G-quadraplex binders

2) DUX4 mRNA and protein
   Antisense technology; CRISPR/Cas13 RNA degradation; degradons/PROTACs

3) *DUX4* downstream pathways
   Anti-inflammatory treatment; anti-oxidants; proteasome

4) *DUX4* modifier genes and factors
   Increase expression of *SMCHD1*, other repressive factors

5) *DUX4*-independent pathways
   Myostatin inhibition; cell and stem cell therapy