Deconstructing the cellular and molecular basis of SBMA motor neuron disease: From mechanism to therapy

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Research Abstract

X-linked spinal and bulbar muscular atrophy (SBMA, Kennedy’s disease) is an inherited neuromuscular disorder characterized by lower motor neuron degeneration. SBMA is caused by

CAG/polyglutamine repeat expansions in the human androgen receptor gene, and is one of nine neurodegenerative disorders that result from polyglutamine (polyQ) proteins. We set out to determine the cellular and molecular basis of SBMA disease pathogenesis. To achieve these goals, we created novel mouse models of SBMA, including BAC transgenic mice containing a floxed first exon (i.e. the BAC fxAR121 line) to permit cell-type specific excision of the AR transgene. We crossed BAC fxAR121 mice with Human Skeletal Actin (HSA)-Cre mice, and documented that excision of the AR transgene from skeletal muscle prevented development of both systemic and neuromuscular SBMA phenotypes, revealing a crucial role for muscle expression of mutant polyQ-AR in SBMA motor neuron degeneration. We produced antisense oligonucleotides (ASOs) directed against AR, and upon peripheral delivery, we demonstrated that peripheral suppression of polyQ-AR rescued motor deficits, reversed alterations in muscle gene expression, and markedly extended lifespan in SBMA mice. These provocative findings implicate skeletal muscle as a key site for SBMA disease pathogenesis. To determine the contribution of motor neurons (MNs) to SBMA, we crossed BAC fxAR121 mice with vChAT-Cre mice, and noted a modest, but significant improvement in motor performance in bigenic mice. Hence, SBMA disease pathogenesis involves a convergence of alterations stemming from pathological interactions between skeletal muscle and MNs. We also uncovered autophagy dysregulation as a defining feature of SBMA MN disease by analyzing in vivo and in vitro models, including a human SBMA stem cell model. These studies revealed abnormalities of autophagosome maturation and lysosome fusion in SBMA cell models, mice, and neuronal progenitor cells derived from iPSCs, thereby linking autophagy dysfunction to the onset of SBMA. To delineate the basis of this effect, we considered the transcriptional regulation of autophagy, uncovered an interaction between AR and transcription factor EB (TFEB), and determined that TFEB dysregulation accounts for autophagy defects in SBMA. In this project, we will define the molecular contributions of skeletal muscle and MNs to SBMA by performing transcriptome analysis in our various conditional deletion SBMA mouse models; delineate the cellular basis for MN demise by developing skeletal muscle and MN models of SBMA from patient iPSCs, and determining if non-cell autonomous toxicity can be recapitulated in these stem cell models; and define the basis for AR co-activation and polyQ-AR repression of TFEB by identifying co-regulators whose interactions and functions with AR and TFEB in complex are altered in the presence of polyQ-AR.

Lay Summary

We have sought the cellular and molecular basis of X-linked spinal & bulbar muscular atrophy (SBMA) by creating novel mouse models of SBMA to permit cell-type specific excision of a polyglutamine-expanded androgen receptor (polyQ-AR) transgene, and thereby documented that excision of the AR transgene from skeletal muscle prevented development of both systemic and neuromuscular SBMA phenotypes and that excision of the AR transgene from motor neurons yielded moderate improvements in SBMA phenotypes, revealing a crucial role for muscle expression of mutant polyQ-AR in SBMA motor neuron disease, but also indicating that motor neuron expression of mutant AR protein contributes to the disease process. We have uncovered abnormalities of autophagosome maturation and lysosome fusion in SBMA cell culture models, transgenic mice, and neuronal progenitor cells derived from patient induced pluripotent stem cells (iPSCs), documented a physical and functional interaction between normal AR and transcription factor EB (TFEB), and determined that TFEB dysregulation accounts for the autophagy defects in SBMA. In this project, we will pursue the basis for pathological interactions between skeletal muscle and motor neurons that conspire to produce

neuron degeneration in SBMA by performing transcriptome analysis of conditional deletion SBMA mice; we will model non-cell autonomous degeneration in iPSC-derived skeletal muscle and motor neurons in conditioned media and co-culture paradigms; and we will determine the basis for AR co-activation of TFEB and polyQ-AR repression of TFEB by defining the normal and mutant AR interactome, and identifying co-regulators whose interactions and functions with AR and TFEB in complex are altered in the presence of polyQ-AR.

Further information available at:

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