

# Fighting polyglutamine disease by wrestling with SUMO

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**Spinobulbar muscular atrophy (SBMA) is an X-linked disease characterized by degeneration of motor neurons, muscle atrophy, and progressive weakness. It is caused by a polyglutamine (polyQ) expansion in the androgen receptor (AR), a transcription factor that is activated upon hormone binding. The polyQ expansion in AR causes it to form intracellular aggregates and impairs transcriptional activity. Intriguingly, SUMOylation (where SUMO indicates small ubiquitin-like modifier) of AR inhibits its transcriptional activity and reduces aggregation of the polyQ form of this protein, but it is unclear whether SUMOylation plays a pathogenic or protective role in SBMA. In this issue of the *JCI*, Chua et al. address this question by generating knockin mice in which the native AR is replaced by either a polyQ AR or a polyQ AR lacking the two lysine residues that are SUMOylated. The results from this study demonstrate that inhibiting SUMOylation of polyQ AR restores much of its transcriptional activity and prevents many (but not all) SBMA-associated symptoms in this mouse model.**

## Polyglutamine disorders and SUMOylation

Patients with spinobulbar muscular atrophy (SBMA) exhibit a progressive loss of muscle function due to motor neuron degeneration. SBMA is the result of a polyglutamine (polyQ) expansion in the androgen receptor (AR) transcription factor. PolyQ AR has reduced transcriptional activity, leading to a toxic gain-of-function effect via disruption of downstream pathways, and is prone to unfolding and oligomerization, resulting in the formation of intracellular aggregates (1). It is currently unclear whether these AR aggregates are directly cytotoxic, and it is also unknown what role the loss of intrinsic AR transcriptional activity plays in SBMA pathogenesis.

SUMOylation is a posttranslational modification of lysine residues in target proteins by the small ubiquitin-like modifier (SUMO), which is a key regulator of multiple cell pathways (2). It is becoming increasingly apparent that SUMOylation

plays important roles in a diverse range of neuronal processes in both health and disease (3). In particular, SUMOylation has been implicated in the pathology of polyQ disorders (4), most notably Huntington's disease, where SUMOylation of huntingtin (HTT) is responsible for the degeneration of striatal neurons (5).

The AR is SUMOylated at two lysine residues, resulting in attenuation of transcriptional activity (6), reduced aggregation of polyQ AR (7), and inhibition of ubiquitination at these lysine residues (8). SUMOylation is unchanged between WT and polyQ forms of AR; therefore, it is not clear whether SUMOylation of polyQ AR contributes to the pathology of SBMA.

In this issue, Chua et al. report on their development of knockin mice in which the native *Ar* locus was replaced with one encoding either a polyQ AR (AR113Q) or a non-SUMOylatable polyQ AR in which lysine residues 385 and 518 were mutated to arginine (AR113Q-KRKR) (9). Because SUMOylation

inhibits AR transcriptional activity, it was predicted that the AR113Q-KRKR mutant would rescue some of the transcription deficiencies caused by AR113Q. This experimental design allowed Chua and colleagues to test whether deficient transcription contributes to SBMA pathology and to determine whether SUMOylation is a potential therapeutic target in SBMA. Additionally, the results provide some insights into the involvement of SUMOylation and polyQ AR aggregation in the disease.

## Is deficient transcriptional regulation responsible for SBMA pathology?

The relative contributions of toxic gain of AR function and loss of intrinsic AR transcriptional activity to the etiology of SBMA have been a matter of some debate. Chua et al. demonstrated that, compared with mice harboring the AR113Q mutation, animals with R113Q-KRKR express many of the genes affected in AR113Q animals (9). These two strains of mice provide a useful tool to study the effects of gain and/or loss of function of AR transcriptional regulation in SBMA. Intriguingly, some, but not all, of the defects in the R113Q mouse model of SBMA could be attributed to the loss of AR-dependent transcriptional activation.

Specifically, survival rates and exercise capacity were severely reduced in AR113Q mice, whereas these parameters were indistinguishable in AR113Q-KRKR mice compared with WT mice (9). Importantly, survival and exercise capacity in castrated AR113Q-KRKR males were similar to AR11Q, demonstrating that amelioration of these symptoms requires the presence of androgen. AR113Q-KRKR mice still exhibited several aspects of polyQ AR-mediated disease, including reduced grip strength and body mass as well as disease onset at the same age as AR113Q mice. Thus, Chua et al. have made some progress toward determining which aspects of SBMA are caused by the loss of transcriptional activity of AR caused by polyQ expansion.

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## How does lack of SUMOylation rescue disease phenotypes?

To better understand how preventing AR SUMOylation might rescue some of the SBMA-associated phenotypes, Chua et al. examined the muscles of the AR113Q and AR113Q-KRKR mice (9). Both AR113Q and AR113Q-KRKR mice displayed muscle loss, with identical levels of atrophy in type II muscle (commonly known as fast-twitch muscle). Interestingly, the degree of atrophy in type I muscle fibers (commonly known as slow-twitch muscle) was greatly reduced in the AR113Q-KRKR animals. Chua and colleagues correlated the difference in type I and type II muscle atrophy to their observation that the AR113Q-KRKR mice have a greatly enhanced cohort of AR-responsive genes, which was highly enriched for genes associated with mitochondria-related functions compared with that of WT and AR113Q mice.

Based on the above observations, Chua et al. argue that the rescue of exercise capacity in the AR113Q-KRKR mice can be attributed to an increase in the expression of genes related to energy production in type I muscle (9). Interestingly, many of the genes detected are differentially expressed between WT and AR113Q-KRKR mice, implying that, rather than directly rescuing AR113Q protein dysfunction, the transcriptional activity of the AR conferred by the prevention of AR113Q SUMOylation upregulates a gene-expression profile that can indirectly compensate for some of the defects resulting from polyQ expansion in the AR. Thus, extreme caution will be required to minimize potential off-target effects of manipulating the SUMOylation pathway should this approach be explored as a therapeutic strategy for SBMA.

It is still not clear how a change in the muscle gene-expression profile was able to rescue the early death phenotype observed in the AR113Q mice. Moreover, humans with SBMA have either a normal or only a slightly reduced life span, suggesting that despite its usefulness, this mouse model, like many disease models, does not fully recapitulate all the features of human SBMA (10).

## Roles of intracellular inclusions

A major unresolved question for many neurodegenerative diseases, including

SBMA, is whether intracellular inclusions of disease-associated protein are directly cytotoxic (11). For SBMA, it has been suggested that SUMOylation reduces aggregation of polyQ AR; however, Chua et al. saw no difference in aggregation between AR113Q and AR113Q-KRKR, implying, at least in this model, that SUMOylation does not regulate protein aggregation (9). A logical extrapolation based on this observation is that polyQ AR inclusions are not responsible for any of the aspects of the disease that can be rescued by AR113Q-KRKR and therefore AR aggregation is not responsible for its loss of function in SBMA. Do these aggregates mediate the proteotoxic gain of function of polyQ AR? The answer to this question remains unclear, although studies have shown little correlation between AR aggregates and neuronal/muscular atrophy in models of SBMA (1), arguing against aggregates promoting the toxic effects of polyQ AR.

## Perspectives: interesting basic science and/or a viable treatment?

In their elegant study, Chua et al. generated a transgenic knockin mouse to dissect the relative contributions of toxic gain of function and loss of function of the polyQ AR in SBMA (9). Using this model, Chua and colleagues demonstrate that increasing the intrinsic transcriptional activation capacity of the AR by inhibiting SUMOylation ameliorates some of the deleterious effects of polyQ AR-mediated disease. Additionally, AR113Q-KRKR-associated improvements were not associated with a decrease in polyQ AR aggregation and inclusion formation. The wider and currently distant question, however, is, does blocking AR SUMOylation represent a viable treatment strategy for sufferers of SBMA? The answer is far from straightforward due to the current lack of pharmacological agents to manipulate SUMOylation in vivo. Furthermore, there are likely to be multiple technical issues that would have to be overcome to successfully design and target such agents to a specific substrate. Given the diverse role of SUMOylation in mammalian cells, such a targeted approach may be necessary to avoid potentially catastrophic effects on vital nuclear and extranuclear functions that require SUMOylation.

While the study by Chua et al. provides molecular insights into cellular mechanisms that underlie SBMA, caution must be used when extrapolating the results obtained in a mouse model to humans affected by SBMA. There are notable differences between this mouse model and the pathology of human SBMA, most importantly the decreased life span of the AR113Q mice. This suggests that the effects of enhancing AR transcriptional activity in patients with SBMA may not provide the same improvements as what was observed in the AR113Q mouse. These caveats notwithstanding, the results of Chua et al. indicate that SUMOylation of polyQ AR does not directly account for the pathology of SBMA. Does this research offer hope of a cure for SBMA? At the moment, it seems not; however, this study has provided new insights into how the various pathological features of the disease are mediated and answered several important questions on the potential roles of SUMOylation in polyQ AR-mediated disease.

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