HIGHLIGHTS

NEURODEGENERATIVE DISEASES

A promising therapy for SBMA

Spinal and bulbar muscular atrophy (SBMA) is caused by the expansion of a polyglutamine-encoding stretch in the androgen receptor gene, and is characterized by the presence of androgen-receptor-containing nuclear inclusions in brainstem and spinal motor neurons. As is the case for every polyglutamine disease, there is no effective treatment for SBMA. However, this situation might change soon, following the report by Katsuno *et al.* in *Nature Medicine* that hormonal therapy with leuprorelin abrogates SBMA phenotypes in a mouse model of the disease.

The authors had previously developed a transgenic mouse model of SBMA by expressing a form of the human androgen receptor with an expanded polyglutamine stretch. This model recapitulates many of the phenotypes that characterize SBMA, including its gender specificity (the disease affects males much more severely than females) and the presence of nuclear inclusions in neurons. Castration leads to symptomatic improvement in the transgenic mice, but in their new study, Katsuno *et al.* set out to find less radical therapeutic alternatives. They turned their attention to two molecules — leuprorelin (a luteinizing hormone-releasing hormone agonist that reduces testosterone release) and flutamide (an androgen antagonist that does not interfere with testosterone release nor with the nuclear translocation of androgen receptors). They found that leuprorelin caused a profound reduction in the number of nuclear inclusions and in the degree of muscle atrophy of the transgenic animals. Moreover, leuprorelin completely eliminated the motor deficits that are found in these mice, and it fully prevented mortality, which reached 100% in untreated animals. By contrast, flutamide had no beneficial effects.

The data of Katsuno *et al.* highlight the importance of the ligand-dependent nuclear translocation of androgen receptors for disease expression, indicating that the pathogenesis of SBMA involves a toxic gain of function of the mutant protein and not the loss of normal receptor function. From the therapeutic angle, leuprorelin is already used in the clinic for the treatment of some types of prostate cancer, although it has side effects such as impotence, osteoporosis and perhaps infertility. But in spite of these undesirable effects, this molecule is the most promising agent to treat SBMA, and the ongoing clinical trial in patients with the condition is fully warranted.

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References and links

ORIGINAL RESEARCH PAPER Katsuno, M. *et al.* Leuprorelin rescues polyglutamine-dependent phenotypes in a transgenic mouse model of spinal and bulbar muscular atrophy. *Nature Med.* 18 May 2003 (doi:101038/nm878)

FURTHER READING Katsuno, M. *et al.* Testosterone reduction prevents phenotypic expression in a transgenic mouse model of spinal and bulbar muscular atrophy. *Neuron* **35**, 943–854 (2002)