

**ASC-J9 ameliorates spinal and bulbar
muscular atrophy phenotype via degradation
of androgen receptor.**

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摘要

Abstract

Motor neuron degeneration resulting from the aggregation of the androgen receptor with an expanded polyglutamine tract (AR-polyQ) has been linked to the development of spinal and bulbar muscular atrophy (SBMA or Kennedy disease). Here we report that adding 5-hydroxy-1,7-bis(3,4-dimethoxyphenyl)-1,4,6-heptatrien-3-one (ASC-J9) disrupts the interaction between AR and its coregulators, and also increases cell survival by decreasing AR-polyQ nuclear aggregation and increasing AR-polyQ degradation in cultured cells. Intraperitoneal injection of ASC-J9 into AR-polyQ transgenic SBMA mice markedly improved disease symptoms, as seen by a reduction in muscular atrophy. Notably, unlike previous approaches in which surgical or chemical castration was used to reduce SBMA symptoms, ASC-J9 treatment ameliorated SBMA symptoms by decreasing AR-97Q aggregation and increasing VEGF164 expression with little change of serum testosterone. Moreover, mice treated with ASC-J9 retained normal sexual function and fertility. Collectively, our results point to a better therapeutic and preventative approach to treating SBMA, by disrupting the interaction between AR and AR coregulators.