AQAMAN: the first compound capable of breaking down ataxin-3 fibrils.

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Abstract:

The Spinocerebellar Ataxia Type 3 (SCA3) is an autosomal, inherited, neurodegenerative disease caused by an abnormal expansion of the polyQ track present in the C-terminal of the ataxin-3 (ATX3) protein. SCA3 is the second polyQ disease for incident worldwide and its principal hallmark is a progressive dysfunction of motor coordination that affect gaze, speech, gait and balance [1] [2]. The onset of SCA3 occurs when the ATX3 polyQ track exceeds the threshold of 55 glutamine residues, and longer is the polyQ track, more severe is the pathology [3].

We employed our ATX3 protein model carrying 55 glutamines (ATX3Q55) to characterize *in vitro* the mode of action of a promising anti-amiloidogenic compound called AQAMAN. Its properties were previously investigated *in vivo* finding that AQAMAN can reduce polyQ aggregation in cell models and ameliorate neurodegeneration in Drosophila SCA3 model [4].

Using both biochemical and biophysical approaches, we demonstrated that AQAMAN slightly accelerates the ATX3-Q55 aggregation rate when added at the beginning of ATX3-Q55 aggregation, with a reduction in the amount of mature fibrils and of intermolecular β-sheet content at the end of the incubation. Using Atomic Force Microscopy we analysed the morphology of ATX3-Q55 aggregates, finding that ATX3-Q55 incubated with AQAMAN did not form mature amyloid fibrils. Moreover, we investigated the disaggregating activity on 48 h pre-formed ATX3-Q55 fibrils treated with AQAMAN for 72 h. The results clearly demonstrated that AQAMAN begin to disaggregate the ATX3-Q55 fibrils immediately after its addition, resealing small structures that present a reduction in mature fibrils content. Noteworthy, to date AQAMAN is the first compound able to break down ATX3 amyloid fibrils.

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