Innovative high throughput screening identifies HSPB8 modulators counteracting misfolded protein accumulation in neurodegenerative diseases

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In different motoneuron diseases it has been demonstrated that overexpression of HSPB8, a key component of the Chaperone-Assisted Selective Autophagy complex, enhance the degradation of misfolded proteins causative of the disease. Therefore, for this type of diseases, could be therapeutically relevant to pharmacologically enhance HSPB8 expression.
We designed a high throughput screening (HTS) able to identify compounds that either enhance HSPB8 gene transcription and/or regulate HSPB8 translation and stability.
The HTS was performed using the compound collection of "Collezione nazionale di composti Chimici e centro screening" (CNCCS) which contains available FDA- and/or EMA-approved drugs and a range of chemotypes, from both commercial and non-commercial suppliers. A collection of 119,059 compounds was tested and, after a secondary dose/response screening, 14 compounds were selected.
All compounds were confirmed to upregulate the endogenous *HSPB8* mRNA and enhanced HSPB8 protein levels. Notably, 4 compounds interfered with the proteasomal degradative pathways, which imply their exclusion as a potential compound of interest, due to the negative impact of proteasome inhibition in those diseases. The formation of mutant SOD1 inclusions, causative of some familial ALS forms, was prevented by 6 compounds and 3 of them were shown not to interfere with the proteasome. Those 3 compounds named C, D and G showed different mechanisms of action. Compounds C acted by stabilizing HSPB8 protein levels and mainly prevented the maturation of mutant SOD1 aggregates to larger complexes, independently by *HSPB8* induction. While compounds D and G, mainly regulated *HSPB8* mRNA levels and prevented the formation of mutant SOD1 aggregates activating also crucial autophagic factors.
In conclusion further studies are needed to clarify which other factors may mediate these differential effects of the three compounds, but they may represent valuable candidates to be tested in pre-clinical studies aimed at counteracting proteotoxic activities in several types of human disorders.

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