Encuentro de Investigación *Buscando sinergias*
Alicante | 7 de junio de 2022 Hospital General Universitario Dr. Balmis de Alicante. Salón de actos. De 10:00 h. a 13:30 h.

Neuronal identity loss in Huntington's disease: Can we recover what is gone?

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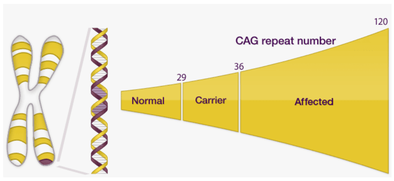
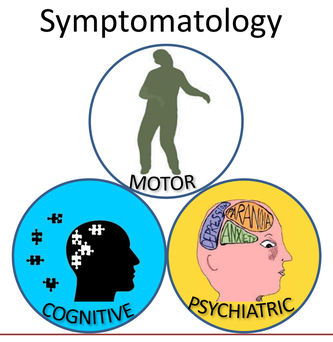
Huntington's disease (HD)

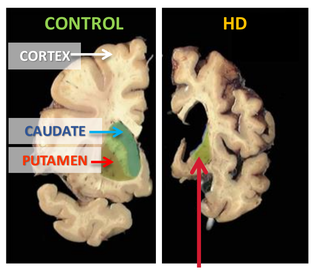
Neuropathological marks of HD: •Prominent striatal atrophy
• Huntingtin aggregates

Genetic expansion of CAG triplet in HTT gene

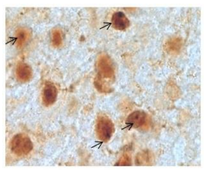


Symptomatology





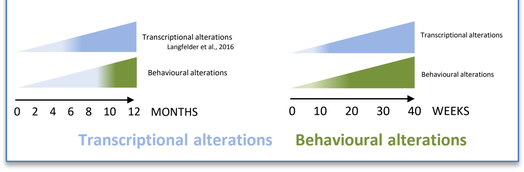
Severe shrinkage of the striatum (caudate/putamen)



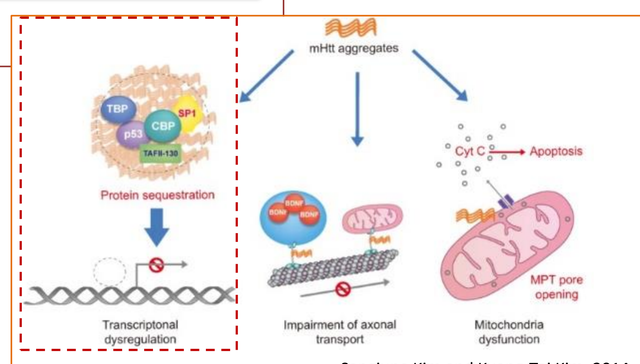
Mutant huntingtin aggregates

Modelling HD with mouse models

Knock-in mice	R6/1 transgenic mice
Mouse htt locus	Exon 1 human mhtt randomly inserted in the genome (trangenic mice)
Exon 1 human mHtt	
Mild phenotype Slow disease progression Better resemble the human mutation	Severe phenotype Fast disease progression



Transcriptional dysregulation in HD



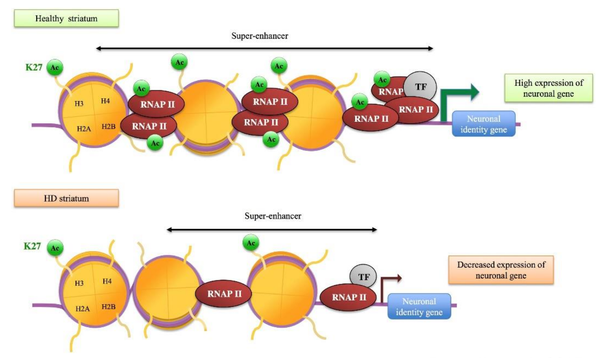
Sangjune Kim and Kyong-Tai Kim, 2014

Transcriptional dysregulation:

- Preserved across mice models and in human patients
- Correlative with disease progression and CAG-length-dependent
- Tissue specific, with major impairment of the striatum

HD transcriptional signature:

- Predominant decrease of neuronal identity genes expression
- Epigenetic dysregulation accompanies the process

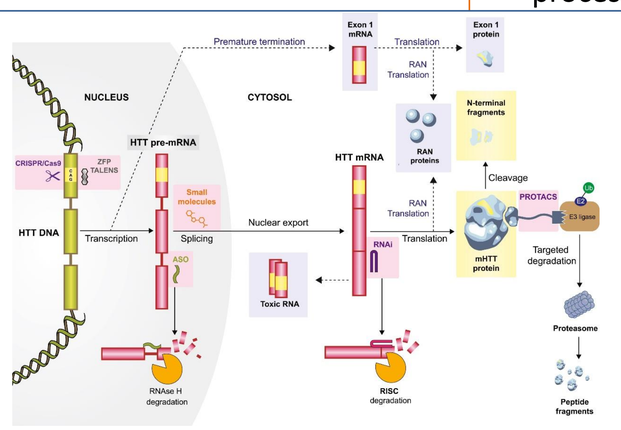


Francelle et al., 2017

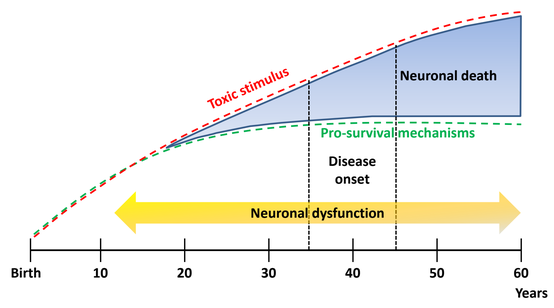
Huntingtin lowering, when to act?

Huntingtin lowering strategies, future perspectives:

- DNA targeting approaches
- RNA targeting approaches
- Approaches to Target Alternative Toxic Species in HD
- Protein Clearance Approaches



Tabrizi et al., 2019



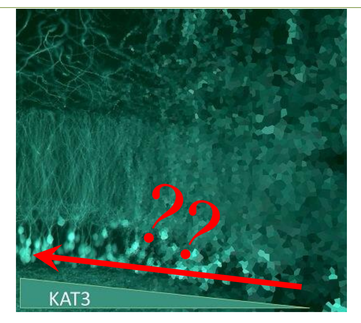
Therapeutic window:

- When to act?
- Can neuronal identity be recovered if mhtt is cleared?

Neuronal identity maintenance… and modulation?

Neuronal identity is actively maintained in the adult brain by the histone lysine acetyl-transferase type 3 (KAT3) proteins:

- KAT3 ablation in adult neurons impairs most significant neuronal processes
- Neuronal identity transcriptional programs are lost in KAT3 ablated adult neurons



Conceptual image illustrating Lipinski et al., 2020

NeuroID3D project: Assessing the impact of KAT3-mediated transient neuronal identity loss in chromatin 3D spatial organization and memory maintenance