MOLECULAR NEURODEGENERATION

LECTURE PRESENTATION Open Access

Novel circuitry and molecular pathogenic mechanisms in Huntington's disease

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From 2011 International Conference on Molecular Neurodegeneration
Shanghai, China. 22-24 September 2011

Background

Huntington's disease (HD) is one of the most common inherited neurodegenerative disorders and is characterized clinically by the mid-age onset of progressive motor, cognitive and psychiatric deficits.

Methods

HD is caused by a CAG repeat expansion encoding an expanded glutamine repeat near the N-terminus of the huntingtin protein. How mutant huntingtin (mhtt) causes progressive and selective degeneration of striatal and cortical neurons, leading to symptoms of HD, remains unclear. In this presentation, I will describe a novel reductionist approach to use Cre/LoxP conditional Bacterial Artificial Chromosome (BAC) transgenic mouse models expressing full-length mhtt to dissect circuitry and molecular pathogenic mechanisms in HD.

Results

Our study defines the distinct but synergistic roles of cortical and striatal projection neurons in HD pathogenesis, and uncovers novel evidence for HD being a non-cell-autonomous disease. Finally, we show that phosphorylation of a small mhtt N-terminus domain can act as a molecular switch to suppress HD pathogenesis *in vivo*.

Conclusion

Together, our studies provide novel mechanistic and therapeutic insights for HD.

Published: 7 February 2012

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doi:10.1186/1750-1326-7-S1-L18
Cite this article as: Yang: Novel circuitry and molecular pathogenic mechanisms in Huntington's disease. *Molecular Neurodegeneration* 2012 **7** (Suppl 1):L18.