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The neuronal kinase DCLK3: Its potential roles in the normal brain and in Huntington's disease

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by an abnormal CAG repeat expansion in the huntingtin (HTT) gene, leading to abnormal poly-glutamine repeats in the huntingtin protein (mHtt) [1]. The main hallmark of HD is the early loss of medium-sized spiny neurons (MSNs) from the striatum. Mutant Htt is toxic to neurons, particularly MSNs, through multiple mechanisms, including altered proteostasis, mitochondrial defects, alteration of trophic factor transport (e.g. BDNF), deregulation of Ca2+ homeostasis, and alteration of survival signaling pathways [2]. mHtt also causes transcriptional anomalies early affecting the expression of a large range of genes [3]. However, none of these mechanisms can account for the preferential damage to the striatum observed early in the disease. Our working hypothesis is that the vulnerability of the striatum in HD is related to the preferential expression of a subset of genes in the MSNs in this brain region. Our lab and others' have shown that indeed, some gene products preferentially expressed in MSN may play a role in the high vulnerability of the striatum [4]. In this presentation, we shall focus on new findings on DCLK3 (Doublecortin-like kinase 3), a kinase preferentially expressed in MSN and neurons of the dentate gyrus of the hippocampus. Its function has never been investigated. The DCLK3 expression is markedly reduced in HD. Thus, we hypothesized that early loss of DCLK3 in HD may render striatal neurons more susceptible to mHtt. We found that DCLK3 silencing in the striatum of mice exacerbated the toxicity of mHtt. Conversely, overexpression of DCLK3 reduced the neurotoxicity of mHtt and reduced motor symptoms in mouse model of HD. Using different mutants of DCLK3, we demonstrated that the kinase activity of the protein plays a crucial role in neuroprotection. We also studied the transcriptional changes produced by the kinase domain in human striatal neurons in culture. Results show that the expression of many genes involved in transcription regulation and nucleosome/chromatin remodeling were regulated by DCLK3 kinase activity. DCLK3 was found to be present in the nucleus of MSN and, protein-protein interaction experiments indicated that the kinase domain interacts with zinc finger proteins, including the transcriptional activator adaptor TADA3, a core component of the Spt-ada-Gcn5 acetyltransferase (SAGA) complex which links histone acetylation to the transcription machinery. Recently, we generated different mice knockout for DCLK3 to further study the roles of this kinase in the brain. Preliminary results show that the downregulation of DCLK3 in the hippocampus could significantly reduce memory performance. Our novel findings suggest that the presence of DCLK3 in neurons may play a key role in transcription regulation and chromatin remodeling. In addition, our findings show that reduced expression of DCLK3 in HD could render the striatum highly vulnerable to neurodegeneration and might also play a role in hippocampal deficits in patients.

Biography

After a PhD in Neuropharmacology at Paris University, Brouillet received post-doctoral fellowships to study Huntington's disease pathogenesis at the Neurology Department of the Mass. General Hospital (Harvard Medical School) where he worked with Professor M Flint Beal. He competed for and obtained a position at the renowned French research organization C.N.R.S in 1993. Since, he dedicated his career to tackle key issues related to neurodegenerative diseases including Huntington's, Parkinson's and Alzheimer's diseases. He also launched a research program on new experimental therapeutics and the development of novel brain imaging methods. He is now Director of Research at C.N.R.S. and is Head of the Neurodegenerative diseases Lab at C.E.A. near Paris. He is the co-author of more than 130 peer-reviewed publications. He teaches Neurosciences at Paris University and also the member of many local and international scientific committees and boards for governmental organizations and charities dedicated to patients with neurodegenerative diseases.

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