Entrega de l'Abstract

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Títol de la recerca: Differential regulation mTORC1 and mTORC2 activity in Huntington's Disease striatum
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Abstract (màxim 500 paraules):

Introduction and aims

Huntington's disease (HD) is a hereditary neurodegenerative disease caused by a CAG repeat expansion in exon-1 of the HD gene resulting in a long polyglutamine tract in the N-terminus of the hungintin protein. This altered protein (mhtt) mainly affects striatal projection neurons but the exact altered molecular mechanisms have not been elucidated yet.

mTOR is a 289 kDa serine/threonine kinase, which is an energetic imbalance sensor and forms the catalytic core of two complexes, the mTOR complex 1 (mTORC1) and 2 (mTORC2). The difference between these complexes is the regulatory accessory protein that mTOR binds, raptor or rictor, respectively. Two mechanisms regulated by mTOR, autophagy and the Akt-survival pathway are altered in HD. So, our aim was to analyze whether these changes were dependent on altered mTOR activity.

Methods

For this study we used the HD mouse model R6/1 expressing N-terminal exon-1 huntingtin with 115 CAG repeats. By Western blot we studied protein levels of total and different phosphorylated forms of mTOR, mTOR substrates, and the two different partners of mTOR, in striatum of R6/1 mice at different stages of disease progression. In addition, we analyzed the intracellular localization of mTOR, and its two phosphorylated forms by immunohistochemistry.

Results

mTOR protein levels were not altered at any of the ages analyzed. In contrast, phospho(Ser2448)mTOR and phospho(Ser2481)mTOR protein levels were increased from 12 weeks of age until the last stage analyzed. In order to determine whether increased mTOR phosphorylation could result in increased activity, we analyzed phospho(Ser757) ULK1/2 as a mTORC1 substrate regulating autophagy. Phospho Ulk1/2 protein levels were not altered in R6/1 mouse striatum at any of the ages analyzed. Moreover rictor, but not raptor, protein levels were increased in the striatum of HD mice at all ages analyzed, and in the putamen of HD patients. Since mTOR has been previously shown to co-localize with mhtt aggregates,

we analyzed whether this also happens for phospho-mTOR by immunohistochemistry. Similar intracellular distribution was detected between wild-type and in the R6/1 mice striatum with no colocalization of phospho mTOR with nuclear mhtt aggregates.

Discussion

Our results showing increased phosphorylated forms of mTOR in the striatum of R6/1 mouse at all the ages analyzed, suggested an overactivation of the mTOR pathway. However, the study of mTORC1 and mTORC2 substrates revealed no changes in phospho(Ser757) ULK1/2 protein levels whereas previous results from our group showed increased levels of phospho(Ser473)Akt levels. These results thus show a possible specific up-regulation of the mTORC2 activity in the R6/1 mouse model of HD, which could be in part due to increased levels of rictor.

The next step of our study is to determinate whether rictor increased levels are accounting for mTORC2 over-activation. To this aim we will analyze mTOR interaction with rictor and raptor by immunoprecipitation and their intracellular localization by immunohistochemistry.

Contribució personal

He realitzat els western blots i les immunohistoquímiques que ens han permès obtenir els resultats. He participat en la recerca bibliogràfica i en la discussió de resultats. Projecte realitzat en 3 mesos.