Phosphoproteomic analysis of TrkB receptor activation by a novel monoclonal antibody agonist: Implications for the treatment of Huntington's disease

Barbara Kracher1, Jan-Philip Schülke1, Nikisha Carty2, Britta Huscher2, Annette Gärtner2, Galina Bunsova2, Tom Schagarus2, Liesbeth Michiels2, Elizabeth van der Kam2, Jonathan Bard3, Jim Rosinski3, Ignacio Munoz-Sanjurjo1, Yahri Beaumont3

1 Evotec Munich GmbH, Am Klopferspitz 19a, 82152 Planegg/Martinsried, Germany
2 CHDI Management/CHDI Foundation, 6080 Center Drive, Suite 700, Los Angeles, CA 90045, USA
3 Evotec SE, Essener Bogen 7, 22419 Hamburg, Germany (Corp. HQ)

Contact: Barbara.Kracher@evotec.com

Introduction

Huntington's disease (HD) is a neurodegenerative disorder caused by CAG expansions in the huntingtin gene (HTT). Alterations of the neurotrophin tyrosine receptor kinase (TrkB) signaling pathway can contribute to HD pathophysiology, as activation of TrkB by brain-derived neurotrophic factor (BDNF) is crucial for the survival, differentiation and synaptic plasticity of striatal neurons. A reduction of BDNF in the striatum, cortex and hippocampus from HD post-mortem brain tissue and reduced cortico-striatal BDNF trafficking in HD mouse models has been described, whilst other reports have demonstrated normal levels of BDNF but impaired downstream TrkB receptor signaling. Here we investigated a potential therapeutic approach to reverse deficits in HD through activation of BDNF/TrkB signaling in an HD mouse model using the novel TrkB agonistic mouse monoclonal antibody 38B8.

Methods

We monitored the effects of the TrkB agonistic antibody 38B8, 4 hours after bilateral intrastriatal injection, on the proteome and phosphoproteome of wild type (WT) and zQ175SDN heterozygous (Q175) mice at 2 months (presymptomatic) and 9 months of age (symptomatic).

Identification of protein expression and phosphorylation changes

While at both ages global striatal protein expression levels were largely unaffected 4 hours after 38B8 injection, we found over 200 significantly regulated phosphorylation sites, mostly exhibiting increased phosphorylation.

Comparison of 38B8 response between WT and Q175 genotypes

The observed changes in protein phosphorylation upon 38B8 treatment were similar between WT and Q175 (HD) mice and no significant differences were detected between the two genotypes.

Conclusion

Taken together, our findings demonstrate the functional activity of 38B8 in an HD mouse model in vivo, which suggests that direct TrkB receptor activation could be a viable approach for the treatment of HD.

Key findings

Sites with significantly increased phosphorylation after 38B8 injection were found on components of all three branches of the BDNF/TrkB (neurophin) signaling pathway and the 38B8 response was similar in WT and Q175 mice of both ages. Thus, our data provides evidence for activation of all three pathway branches in both wild-type and Q175 (HD) mice.

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