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Silencing ataxin-3 mitigates degeneration in a rat model of Machado-Joseph disease: no role for wild-type ataxin-3?

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Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière
INSERM UMRS 975 (ex U769) - CNRS UMR 7225- Université Pierre et Marie Curie
Hôpital de la Salpêtrière
Institut du Cerveau et de la Moelle épinière
47, Bd de l'Hôpital,
75651 Paris Cedex 13
France
Telephone: +33(0)1 57 27 46 65
E-mail: sandropfalves@gmail.com
And
Center for Neurosciences & Cell Biology
Faculty of Pharmacy and Faculty and Technology
University of Coimbra
Coimbra - Portugal

About the work

Machado–Joseph disease or spinocerebellar ataxia type 3 (MJD/SCA3) is a fatal, autosomal dominant disorder caused by a cytosine-adenine-guanine expansion in the coding region of the MJD1 gene. RNA interference has potential as a therapeutic approach for MJD but raises the issue of the role of wild-type ataxin-3 (WT ATX3) in MJD and of whether the expression of the wild-type protein must be maintained. Taking advantage of the presence of a single nucleotide polymorphism in linkage disequilibrium with the

disease-causing CAG expansion, a siRNA specifically targeting the mutant allele has been developed. Allele-specific silencing of ataxin-3 using lentiviral vectors (LVs) significantly decreased the severity of the neuropathological abnormalities in a rat model of MJD. This approach is particularly attractive because the WT ATX3 allele is not targeted and consequently its normal functions are unaffected. However, this therapy would benefit ~70% of MJD patients at best. Whether a silencing not discriminating between wild-type and mutant alleles would be of benefit remained to be determined. Here, we report an investigation of the contribution of WT ATX3 to MJD.
To address this issue, we constructed LVs allowing either the overexpression of wild-type human ataxin-3 or the silencing of endogenous ataxin-3 and studied their effects in a rat model of MJD. We showed that (i) overexpression of WT ATX3 did not protect against MJD pathology, (ii) knockdown of WT ATX3 did not aggravate MJD pathology and that (iii) non-allele-specific silencing of ataxin-3 strongly reduced neuropathology in a rat model of MJD. The absence of a role for WT ATX3 in this experimental paradigm justified the investigation of a global silencing of mutant and WT ATX3, which led to robust reduction of neurodegeneration. Our findings indicate that therapeutic strategies involving non-allele-specific silencing to treat MJD patients may be safe and effective.

About the author

Sandro Alves earned his PhD (2008) from the Faculty of Pharmacy of the University of Coimbra and Center for Neuroscience and Cell Biology of Coimbra in collaboration with the *Commissariat à L'Énergie Atomique* (CEA), Institute of Biomedical Imaging (I2BM) and Molecular Imaging Research Center (MIRCen), Fontenay-aux-Roses, Paris, France. Sandro Alves focused his PhD research on the "Modelling and Gene silencing in Machado-Joseph disease" under supervision of Prof. Luis Pereira de Almeida and Dr. Nicole Déglon, developing a lentiviral-based animal model of Machado-Joseph disease / Spinocerebellar ataxia type 3 and evaluating pre-clinical therapeutic strategies based on gene silencing - RNA interference (RNAi). His work has been published in peer-reviewed international research journals, such as *Human Molecular Genetics*, *PLoS ONE* and *Annals of Neurology*.
During his PhD, Sandro Alves has also made contributions to the fields of gene therapy and gene transfer in Huntington's disease, another polyglutamine disorder. His research interests mainly focus on gene therapy in the central nervous system using lentiviral vectors and gene silencing to promote neuroprotection.
The research of Sandro Alves has already been recognized with several prizes:
-Portuguese Society of Neuroscience (SPN), in 2009, recognizing a paper published in the journal *Human Molecular Genetics*- category: Neurobiology of diseases (Alves et al. 2008);
-Portuguese Society of Human Genetics (SPGH), in 2009, that recognizes the first author of the best portuguese paper published in the journal PLoS ONE, in 2008, in the field of human medical genetics (Prize SPGH 2009) (Alves et al. 2008b).
Presently, Sandro Alves has a post-doctoral position in the CRICM - *Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière*, in the Unit INSERM U975 "Molecular basis, physiopathology and treatment of neurodegenerative diseases", in the hospital P*itié-Salpêtrière*, Université Pierre et Marie Curie- Paris VI, Paris, France, where he is currently working on the development of pre-clinical gene silencing strategies as therapeutic approaches to counteract Spinocerebellar ataxia type 7, another polyglutamine disease that causes severe cerebellar ataxia and retinal degeneration.