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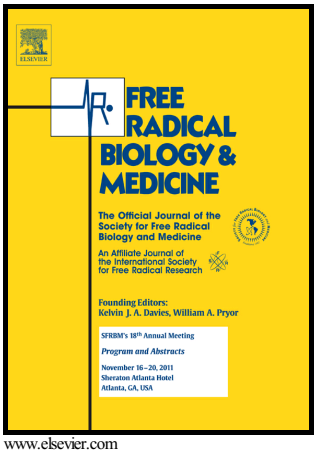

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An innate immune response and altered nuclear receptor activation defines the spinal cord transcriptome during alpha-tocopherol deficiency in *Ttpa*-null mice

Carrie J. Finno[1]*, Matthew H. Bordbari[1], Giuliana Gianino[1], Brittni Ming-Whitfield[1], Erin Burns[1], Janel Merkel[1], Monica Britton[2], Blythe Durbin-Johnson,[2] Erica A. Sloma,[3] Marissa McMackin,[4] Gino Cortopassi,[4] Victor Rivas[1], Marietta Barro,[1] Cecilia K. Tran,[5] Ingrid Gennity,[4] Hadi Habib,[4] Libin Xu,[5] Birgit Puschner,[4] Andrew D. Miller[3]

[1]Department of Population Health and Reproduction, School of Veterinary Medicine, University of California, Davis CA USA 95616

[2]Bioinformatics Core Facility, Genome Center, University of California, Davis CA USA 95616

[3] Department of Biomedical Sciences, Section of Anatomic Pathology, Cornell University College of Veterinary Medicine, Ithaca, NY 14853

[4]Department of Molecular Biosciences, School of Veterinary Medicine, University of California, Davis CA USA 95616

*Corresponding author: University of California, Davis SVM, Room 4206 Vet Med 3A, One Shields Ave, Davis, CA 95616. Tel.: (530) 752 2739. cjfinno@ucdavis.edu

Abstract

Mice with deficiency in tocopherol (alpha) transfer protein gene develop peripheral tocopherol deficiency and sensory neurodegeneration. *Ttpa*$^{-/-}$ mice maintained on diets with deficient α-tocopherol (α-TOH) had proprioceptive deficits by six months of age, axonal degeneration and neuronal chromatolysis within the dorsal column of the spinal cord and its projections into the medulla. Transmission electron microscopy revealed degeneration of dorsal column axons. We addressed the potential pathomechanism of α-TOH deficient neurodegeneration by global transcriptome sequencing within the spinal cord and cerebellum. RNA-sequencing of the spinal cord in *Ttpa*$^{-/-}$ mice revealed upregulation of genes associated with the innate immune response, indicating a molecular signature of microglial activation as a result of tocopherol deficiency. For the first time, low level *Ttpa* expression was identified in the murine spinal cord. Further, the transcription factor liver X receptor (LXR) was strongly activated by α-TOH deficiency, triggering dysregulation of cholesterol biosynthesis. The aberrant activation of transcription factor LXR suppressed the normal induction of the transcription factor retinoic-related orphan receptor-α (RORA), which is required for neural homeostasis. Thus we find that α-TOH deficiency induces LXR, which may lead to a molecular signature of microglial activation and contribute to sensory neurodegeneration.

Abbreviations:

3-NT, 3-nitrotyrosine; α-TOH, Alpha-tocopherol; AVED, Ataxia with vitamin E deficiency; CNS, Central nervous system; DET, Differentially expressed transcript; GFAP, Glial fibrillary acidic protein; HE, Hematoxylin and eosin; IHC, Immunohistochemistry; LXR, Liver X receptor; MPM, Meters per minute; RORA, Retinoic-related orphan receptor-α; RXR, Retinoid X receptor; TBARS, Thiobarbituric acid; TEM, Transmission electron microscopy; t-HODE, Total hydroxyoctadecadienoic acids; TTP, Tocopherol (alpha) transfer protein; VitE, Vitamin E

Keywords: RNA-sequencing; transcription; vitamin E

Introduction

Free radical-mediated oxidation products highly correlate with the pathogenesis and progression of many diseases including Alzheimer's disease, Down syndrome, Parkinson's disease, and