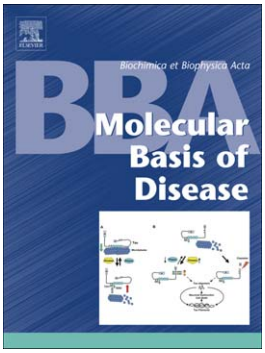

Lysine deacetylases and mitochondrial dynamics in neurodegeneration

Pedro Guedes-Dias, Jorge M.A. Oliveira

PII: S0925-4439(13)00108-7
DOI: doi: 10.1016/j.bbadis.2013.04.005
Reference: BBADIS 63682

To appear in: *BBA - Molecular Basis of Disease*

Received date: 30 December 2012
Revised date: 30 March 2013
Accepted date: 2 April 2013

Please cite this article as: Pedro Guedes-Dias, Jorge M.A. Oliveira, Lysine deacetylases and mitochondrial dynamics in neurodegeneration, *BBA - Molecular Basis of Disease* (2013), doi: 10.1016/j.bbadis.2013.04.005

Lysine deacetylases and mitochondrial dynamics in neurodegeneration

Pedro Guedes-Dias, Jorge M. A. Oliveira*

REQUIMTE, Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal

*Corresponding author at: Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Rua Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal, Tel. +351 220 428 610; Fax: +351 226 093 390; E-mail: jorgemao@ff.up.pt

ABSTRACT

Lysine acetylation is a key post-translational modification known to regulate gene transcription, signal transduction, cellular transport and metabolism. Lysine deacetylases (KDACs), including classical KDACs (a.k.a. HDACs) and sirtuins (SIRTs), are emerging therapeutic targets in neurodegeneration. Given the strong link between abnormal mitochondrial dynamics and neurodegenerative disorders (e.g. in Alzheimer, Parkinson and Huntington diseases), here we examine the evidence for KDAC-mediated regulation of mitochondrial biogenesis, fission-fusion, movement and mitophagy. Mitochondrial biogenesis regulation was reported for SIRT1, SIRT3, and class IIa KDACs, mainly via PGC-1α modulation. SIRT1 or SIRT3 overexpression rescued mitochondrial density and fission-fusion balance in neurodegeneration models. Mitochondrial fission decreased with pan-classical-KDAC inhibitors and increased with nicotinamide (pan-sirtuin-inhibitor/activator depending on concentration and NAD^+ conversion). Mitochondrial movement increased with HDAC6 inhibition, but this is not yet reported for the other tubulin deacetylase SIRT2. Inhibition of HDAC6 or SIRT2 was reported neuroprotective. Mitophagy is assisted by the HDAC6 ubiquitin-binding and autophagosome-lysosome fusion promoting activities, and was also associated with SIRT1 activation. In summary, KDACs can potentially modulate multiple components of mitochondrial dynamics, however, several key points require clarification. The SIRT1-biogenesis connection relies heavily in controversial caloric restriction (CR) regimes or CR-mimetic drugs, and appears cell-type dependent, recommending caution before linking SIRT1 activation with general neuroprotection. Future studies should clarify mitochondrial fission-fusion regulation by KDACs, and the