HDAC6 mutations rescue human tau-induced microtubule defects in *Drosophila*

Ying Xiong[a], Kai Zhao[a], Jiaxi Wu[a,1], Zhiheng Xu[a], Shan Jin[b] and Yong Q. Zhang[a,2]

[a]Key Laboratory of Molecular and Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing 100101, China

[b]College of Life Sciences, Hubei University, Wuhan, Hubei 430062, China

Author contributions: Y.X. and Y.Q.Z. designed research; Y.X., K.Z., J.W., and S.J. performed research; Y.X., K.Z., and Z.H.X. analyzed data; and Y.X. and Y.Q.Z. wrote the paper.

[1]Present address: Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA.

[2]To whom correspondence should be addressed. E-mail: yqzhang@genetics.ac.cn.

Abstract

Neurons from the brains of Alzheimer's disease (AD) and related tauopathy patients contain neurofibrillary tangles composed of hyperphosphorylated tau protein. Tau normally stabilizes microtubules (MTs); however, tau hyperphosphorylation leads to loss of this function with consequent MT destabilization and neuronal dysfunction. Accordingly, MT-stabilizing drugs such as paclitaxel and epothilone D have been shown as possible therapies for AD and related tauopathies. However, MT-stabilizing drugs have common side-effects such as neuropathy and neutropenia. To find new suppressors of tau-induced MT defects, we established a *Drosophila* model ectopically expressing human tau in muscle cells, which allow for clear visualization of MT network. Overexpressed tau was hyperphosphorylated and resulted in decreased MT density and greater fragmentation, consistent with previous reports in AD patients and mouse models. From a genetic screen, we found that an *HDAC6* (*histone deacetylase 6*) null mutation rescued tau-induced MT defects in both muscles and neurons. Genetic and pharmacological inhibition of the tubulin-specific deacetylase activity of HDAC6 demonstrates that the rescue effect is mediated primarily by increased MT acetylation. These findings reveal HDAC6 as a novel potential drug target for AD and related tauopathies.

Key words: microtubule; tau; acetylation; HDAC6; *Drosophila*