Article

SOURCE DATA | TRANSPARENT PROCESS

THE EMBO JOURNAL

Leucine-rich repeat kinase 2 regulates Sec16A at ER exit sites to allow ER–Golgi export

Hyun Jin Cho[1], Jia Yu[1], Chengsong Xie[1], Parvathi Rudrabhatla[2], Xi Chen[1], Junbing Wu[1], Loukia Parisiadou[1], Guoxiang Liu[1], Lixin Sun[1], Bo Ma[1], Jinhui Ding[3], Zhihua Liu[4,5,*] & Huaibin Cai[1,**]

Abstract

Leucine-rich repeat kinase 2 (LRRK2) has been associated with Parkinson's disease (PD) and other disorders. However, its normal physiological functions and pathogenic properties remain elusive. Here we show that LRRK2 regulates the anterograde ER–Golgi transport through anchoring Sec16A at the endoplasmic reticulum exit sites (ERES). LRRK2 interacted and co-localized with Sec16A, a key protein in the formation of ERES. Lrrk2 depletion caused a dispersion of Sec16A from ERES and impaired ER export. In neurons, LRRK2 and Sec16A showed extensive co-localization at the dendritic ERES (dERES) that locally regulate the transport of proteins to the dendritic spines. A loss of Lrrk2 affected the association of Sec16A with dERES and impaired the activity-dependent targeting of glutamate receptors onto the cell/synapse surface. Furthermore, the PD-related LRRK2 R1441C missense mutation in the GTPase domain interfered with the interaction of LRRK2 with Sec16A and also affected ER–Golgi transport, while LRRK2 kinase activity was not required for these functions. Therefore, our findings reveal a new physiological function of LRRK2 in ER–Golgi transport, suggesting ERES dysfunction may contribute to the pathogenesis of PD.

Keywords dendritic ERES (dERES); ER exit sites (ERES) ; ER–Golgi transport; Leucine-rich repeat kinase 2 (LRRK2); Sec16A
Subject Categories Membrane & Intracellular Transport; Neuroscience
DOI 10.15252/embj.201487807 | Received 2 January 2014 | Revised 7 July 2014 | Accepted 13 August 2014 | Published online 8 September 2014
The EMBO Journal (2014) 33: 2314–2331

See also: **B Lu** (October 2014)

Introduction

Missense mutations in *LRRK2* have been initially linked to a late-onset autosomal dominant form of familial Parkinson's disease (PD) (Paisan-Ruiz *et al*, 2004; Zimprich *et al*, 2004). The genome-wide association studies have further revealed that *LRRK2* gene loci are also associated with sporadic PD, Crohn's disease, and leprosy (Barrett *et al*, 2008; Satake *et al*, 2009; Simon-Sanchez *et al*, 2009; Zhang *et al*, 2009). *LRRK2* encodes a large multi-domain protein, containing one Ras of complex GTPase (ROC) domain, one serine/threonine kinase domain, and multiple protein–protein interaction domains (Mata *et al*, 2006). LRRK2 has been shown to regulate a variety of cellular events, such as microtubule and actin cytoskeleton assembly, protein translation, microRNA maturation, nuclear factor of activated T-cells (NFAT) signaling, endocytosis, neuronal morphogenesis, and autophagy/lysosome-mediated protein degradation (Jaleel *et al*, 2007; Gandhi *et al*, 2008; Imai *et al*, 2008; Plowey *et al*, 2008; Lin *et al*, 2009; Parisiadou *et al*, 2009, 2014; Liu *et al*, 2011; Matta *et al*, 2012; Orenstein *et al*, 2013). In addition, our previous study in transgenic mice demonstrates that overexpression of LRRK2 causes Golgi fragmentation in neurons (Lin *et al*, 2009). PD-related-α-synuclein has also been shown to block ER–Golgi transport by inhibiting the docking and fusion of coat protein complex II (COPII) vesicles with Golgi apparatus (Cooper *et al*, 2006; Gitler *et al*, 2008). However, how LRRK2 regulates ER–Golgi trafficking is unclear.

ER–Golgi export is initiated by formation and secretion of COPII vesicles at the specialized ER domains, namely ER exit sites (ERES) or transitional ER (tER) (Miller & Barlowe, 2010; Zanetti *et al*, 2012). ER-associated membrane protein Sec12 mediates the assembly of COPII vesicles at ERES by activating GTPase Sar1, which subsequently recruits inner layer heterodimer protein complex Sec23 and Sec24 (Sec23/24) as well as outer layer protein complex Sec13 and Sec31 (Sec13/31) for the capture of cargo proteins into nascent buds and formation of a structural cage around the budding vesicles, respectively (Zanetti *et al*, 2012). Additionally, Sec16A, a large hydrophilic peripheral membrane protein, has been identified recently as an essential component required for the formation of ERES and COPII vesicle trafficking (Espenshade *et al*, 1995; Connerly *et al*, 2005; Watson *et al*, 2006; Hughes *et al*, 2009). However, what acts at the upstream of Sec16A that regulates the recruitment of Sec16A onto ERES is poorly understood (Miller & Barlowe, 2010).

1 Transgenics Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA
2 Laboratory of Neurochemistry and Laboratory of Neurobiology, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA
3 Bioinformatics Core, Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA
4 Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA
5 Institute of Biophysics, Chinese Academy of Sciences, Beijing, China
*Corresponding author. Tel: +8 610 648 88428; Fax: +8 610 648 71293; E-mail: zhihualiu@ibp.ac.cn
**Corresponding author. Tel: +1 301 402 8087; Fax: +1 301 480 2830; E-mail: caih@mail.nih.gov