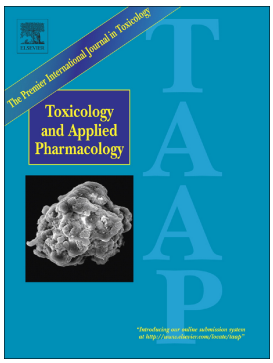

Topovectorial mechanisms control the juxtamembrane proteolytic processing of Nrf1 to remove its N-terminal polypeptides during maturation of the CNC-bZIP factor

Yuancai Xiang, Josefin Halin, Zhuo Fan, Shaofan Hu, Meng Wang, Lu Qiu, Zhengwen Zhang, Peter Mattjus, Yiguo Zhang

PII: S0041-008X(18)30444-7
DOI: doi:10.1016/j.taap.2018.09.039
Reference: YTAAP 14418

To appear in: *Toxicology and Applied Pharmacology*

Received date: 26 June 2018
Revised date: 17 September 2018
Accepted date: 26 September 2018

Please cite this article as: Yuancai Xiang, Josefin Halin, Zhuo Fan, Shaofan Hu, Meng Wang, Lu Qiu, Zhengwen Zhang, Peter Mattjus, Yiguo Zhang , Topovectorial mechanisms control the juxtamembrane proteolytic processing of Nrf1 to remove its N-terminal polypeptides during maturation of the CNC-bZIP factor. Ytaap (2018), doi:10.1016/j.taap.2018.09.039

Topovectorial mechanisms control the juxtamembrane proteolytic processing of Nrf1 to remove its N-terminal polypeptides during maturation of the CNC-bZIP factor

Yuancai Xiang[1], Josefin Halin[2], Zhuo Fan[1], Shaofan Hu[1], Meng Wang[1], Lu Qiu[1], Zhengwen Zhang[3], Peter Mattjus[2], and Yiguo Zhang[1]*

[1]The Laboratory of Cell Biochemistry and Topogenetic Regulation, College of Bioengineering and Faculty of Sciences, Chongqing University, No. 174 Shazheng Street, Shapingba District, Chongqing 400044, China; [2]Department of Biochemistry, Faculty of Science and Engineering, Åbo Akademi University, Artillerigatan 6A, III, BioCity, FI-20520 Turku, Finland; [3]Institute of Neuroscience and Psychology, School of Life Sciences, University of Glasgow, 42 Western Common Road, G22 5PQ, Glasgow, Scotland, United Kingdom.

*Correspondence should be addressed to Yiguo Zhang (Email: yiguozhang@cqu.edu.cn, or eaglezhang64@gmail.com)

ABSTRACT

The topobiological behaviour of Nrf1 dictates its post-translational modification and its ability to transactivate target genes. Here, we have elucidated that topovectorial mechanisms control the juxtamembrane processing of Nrf1 on the cyto/nucleoplasmic side of endoplasmic reticulum (ER), whereupon it is cleaved and degraded to remove various lengths of its N-terminal domain (NTD, also refold into a UBL module) and acidic domain-1 (AD1) to yield multiple isoforms. Notably, an N-terminal ~12.5-kDa polypeptide of Nrf1 arises from selective cleavage at an NHB2-adjoining region within NTD, whilst other longer UBL-containing isoforms may arise from proteolytic processing of the protein within AD1 around PEST1 and Neh2L degrons. The susceptibility of Nrf1 to proteolysis is determined by dynamic repositioning of potential UBL-adjacent degrons and cleavage sites from the ER lumen through p97-driven retrotranslocation and -independent pathways into the cyto/nucleoplasm. These repositioned degrons and cleavage sites within NTD and AD1 of Nrf1 are coming into their *bona fide* functionality, thereby enabling it to be selectively processed by cytosolic DDI-1/2 proteases and also degraded *via* 26S proteasomes. The resultant proteolytic processing of Nrf1 gives rise to a mature ~85-kDa CNC-bZIP transcription factor, which regulates transcriptional expression of cognate target genes. Furthermore, putative ubiquitination of Nrf1 is not a prerequisite necessary for involvement of p97 in the client processing. Overall, the regulated juxtamembrane proteolysis (RJP) of Nrf1, though occurring in close proximity to the ER, is distinctive from the mechanism that regulates the intramembrane proteolytic (RIP) processing of ATF6 and SREBP1.

Keywords: Nrf1, topovectorial regulation, regulated juxtamembrane proteolysis, ubiquitination, topobiology