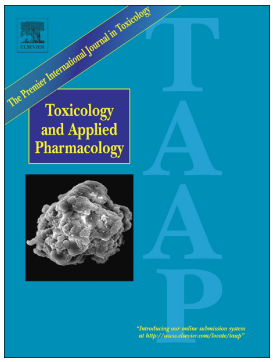

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Mechanisms controlling the multistage post-translational processing of endogenous Nrf1α/TCF11 proteins to yield distinct isoforms within the coupled positive and negative feedback circuits

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ABSTRACT

To gain a better understanding of the multistep processing of Nrf1 to yield various isoforms with confused molecular masses, we herein establish a generally acceptable criterion required for identification of its endogenous full-length proteins and derivative isoforms expressed differentially in distinct experimental cell lines. Further work has been focused on the molecular mechanisms that dictate the successive post-translational modifications (i.e. glycosylation by OST, deglycosylation by NGLY, and ubiquitination by Hrd1) of this CNC-bZIP protein and its proteolytic processing to give rise to multiple proteoforms. Several lines of experimental evidence have demonstrated that the nascent Nrf1α/TCF11 polypeptide (non-glycosylated) is transiently translocated into the endoplasmic reticulum (ER), in which it becomes an inactive glycoprotein-A, and is folded in a proper topology within and around membranes. Thereafter, dynamic repositioning of the ER-resident domains in Nrf1 glycoprotein is driven by p97-fueled retrotranslocation into extra-ER compartments. Therein, Nrf1 glycoprotein is allowed for deglycosylation digestion by glycosidases into a deglycoprotein-B and its progressive proteolytic processing by cytosolic DDI-1/2 and proteasomes so as to generate N-terminally-truncated protein-C/D. This processing is accompanied by removal of a major N-terminal ~12.5-kDa polypeptide from Nrf1α. Interestingly, our present study has further unraveled that there exist coupled positive and negative feedback circuits between Nrf1 and cognate target genes, including those encoding its regulators p97, Hrd1, DDI-1 and proteasomes. These key players are differentially or even oppositely involved in diverse cellular signalling responses to distinct extents of ER-derived proteotoxic and oxidative stresses induced by different concentrations of proteasomal inhibitors.

Key words: Nrf1, DDI-1/2, p97, proteoforms, proteasome, post-translational modification, proteolysis, ER stress