A systematic search for endoplasmic reticulum (ER) membrane-associated RING finger proteins identifies Nixin/ZNRF4 as a regulator of calnexin stability and ER homeostasis

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To identify novel regulators of endoplasmic reticulum (ER)-linked protein degradation and ER function, we determined the entire inventory of membrane-spanning RING finger E3 ubiquitin ligases localized to the ER. We identified 24 ER membrane-anchored ubiquitin ligases and found Nixin/ZNRF4 to be central for the regulation of calnexin turnover. Ectopic expression of wild type Nixin induced a dramatic down-regulation of the ER-localized chaperone calnexin that was prevented by inactivation of the Nixin RING domain. Importantly, Nixin physically interacts with calnexin in a glycosylation-independent manner, induces calnexin ubiquitination, and p97-dependent degradation, indicating an ER-associated degradation-like mechanism of calnexin turnover.

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