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Mechanisms of endoplasmic reticulum-associated degradation (ERAD-l) of glycoproteins and non-glycoproteins

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Glycoproteins and non-glycoproteins possessing unfolded/misfolded part(s) in their luminal regions are cleared from the endoplasmic reticulum (ER) by ER-associated degradation (ERAD)-L with distinct mechanisms. Two-step mannose trimming from $Man_9GlcNAc_2$ is crucial in the ERAD-L of glycoproteins. Htm1-mediated mannose trimming from the oligosaccharide $Man_8GlcNAc_2$ to $Man_7GlcNAc_2$ is the rate-limiting step in yeast. In contrast, the roles of the three Htm1 homologues (EDEM1/2/3) in mammalian gpERAD have remained elusive, with a key controversy being whether EDEMs function as mannosidases or as lectins. We therefore conducted TALEN-mediated gene knockout analysis in human cell line and found that all endogenous EDEMs possess mannosidase activity. Mannose trimming from $Man_8GlcNAc_2$ to $Man_7GlcNAc_2$ is carried out mainly by EDEM3 and to a lesser extent by EDEM1. Most surprisingly, the upstream mannose trimming from $Man_9GlcNAc_2$ to $Man_8GlcNAc_2$ is conducted mainly by EDEM2, which was previously considered to lack enzymatic activity. We further constructed human cells simultaneously deficient in EDEM1/2/3, and analyzed the fates of four ERAD-L substrates containing three potential N-glycosylation sites. We found that native but unstable or somewhat unfolded glycoproteins, such as ATF6α, ATF6α(C), CD3-δ—Δ□□ and EMC1,were stabilized in EDEM1/2/3-triple knockout cells. In marked contrast, degradation of severely misfolded glycoproteins, such as NHK and deletion or insertion mutants of ATF6α(C), CD3-δ—Δ□□ and EMC1, was delayed only at early chase periods, but they were eventually degraded as in wild-type cells. Thus, higher eukaryotes are able to extract severely misfolded glycoproteins from glycoprotein ERAD, and target them to the non-glycoprotein ERAD pathway to maintain the homeostasis of the ER.

Biography

Kazutoshi Mori is Professor at the Graduate School of Science, Kyoto University since 2003. He graduated from the Graduate School of Pharmaceutical Sciences, Kyoto University. He was Instructor at Gifu Pharmaceutical University from 1985 to 1989, and then worked as a postdoctoral fellow at the University of Texas Southwestern Medical Center at Dallas from 1989 to 1993 (under supervision from Drs. Gething and Sambrook). He was Research Manager from 1993 to 1999 at the HSP Research Institute in Kyoto (directed by Dr. Yura). He was Associate Professor at the Graduate School of Biostudies, Kyoto University from 1999 to 2003.

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