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RENAL PHYSIOLOGY

ER-associated degradation in diabetes insipidus

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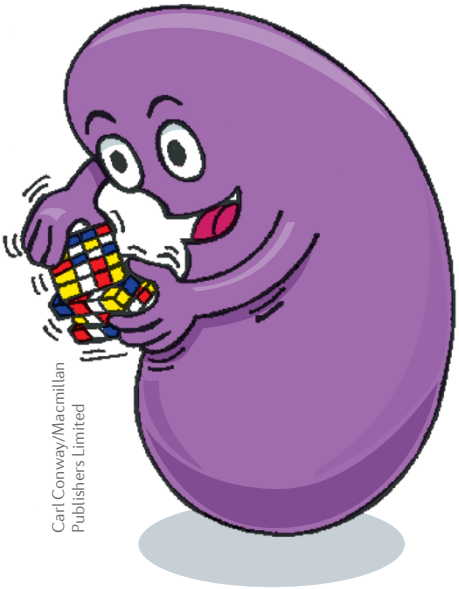

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Diabetes insipidus is a disorder characterized by polydipsia and polyuria, and is caused by a deficiency of the antidiuretic hormone arginine vasopressin (AVP) or a defective renal response to AVP. New findings have revealed a role for endoplasmic reticulum-associated degradation (ERAD) in the maturation and processing of the AVP precursor prohormone proAVP, demonstrating that dysfunctional activity of the ERAD protein complex SEL1L–HRD1, causes retention and aggregation of proAVP in the ER, leading to a diabetes insipidus phenotype in mice. "This study points to a previously unappreciated signalling pathway linking ERAD to systemic water homeostasis and prohormone maturation," explains researcher Ling Qi from the University of Michigan Medical School. "While it is not surprising that ERAD degrades a fraction of newly synthesized, unstable proAVP, it is unexpected that ERAD deficiency would cause ER retention and aggregation of a large proportion of proAVP protein *in vivo*."

Several peptide hormones, including AVP, are synthesized in the ER as prohormones before being activated by proteolytic cleavage and released into the circulation. The importance of appropriate protein folding and processing in this process is exemplified by the finding that mutations in proAVP lead to retention of the prohormone in the ER and the development of diabetes insipidus; however, the molecular mechanisms that regulate proAVP folding and degradation in the ER are largely unknown. Qi states that their initial insights into these mechanisms arose from the serendipitous observation that mice with global inducible deletion of the ERAD protein SEL1L had polydipsia, polyuria and decreased urine osmolality, which are consistent with diabetes insipidus.Further characterization of these mice revealed that the phenotype was the result of a central defect rather than a defect in renal urine-concentrating ability, and could be rescued by administration of the vasopressin receptor agonist dDAVP. "In other words, the AVP-producing neurons, rather than the kidneys, were responsible for diabetes insipidus induced by SEL1L deficiency," explains Qi. "Indeed, we show that AVP-neuron-specific *Sel1L*-knockout mice are a phenocopy of the global inducible knockout model."

To investigate the mechanisms by which SEL1L deficiency induces diabetes insipidus, the researchers assessed the level and distribution of proAVP protein in AVP neurons of wild-type and AVP-neuron-specific *Sel1L*-knockout mice. Consistent with decreased circulating levels of AVP in the knockout mice, the researchers noted a decrease in AVP levels in the axons of SEL1L-deficient neurons, suggesting dysfunctional cleavage and processing of the proAVP precursor peptide. In agreement with these findings, imaging and biochemical analyses demonstrated that a deficiency of SEL1L or its co-complex protein HRD1 causes retention of proAVP in the ER. This retention is induced by the formation of an aggregation of proAVP complexes, resulting from the formation of erroneous intermolecular disulfide bonds in a process mediated by the protein disulfide isomerase PDI. "We have therefore identified an important role for intermolecular disulfide bonds and the redox activity of PDI in disease pathogenesis induced by ERAD deficiency," says Qi. "In the absence of SEL1L–HRD1, misfolded proAVP proteins with highly reactive cysteine thiols are generated, which participate in the formation of inappropriate disulfide-bonded aggregates in a process promoted by the enzymatic activity of PDI."

The finding that proAVP is a novel endogenous substrate of ERAD has prompted Qi and colleagues to assess whether ERAD is a general mechanism involved in prohormone maturation. "In addition, my collaborators and I plan to assess whether ERAD and other ER quality control mechanisms interact in prohormone processing and in the pathogenesis of diabetes insipidus," notes Qi.

Susan J. Allison

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