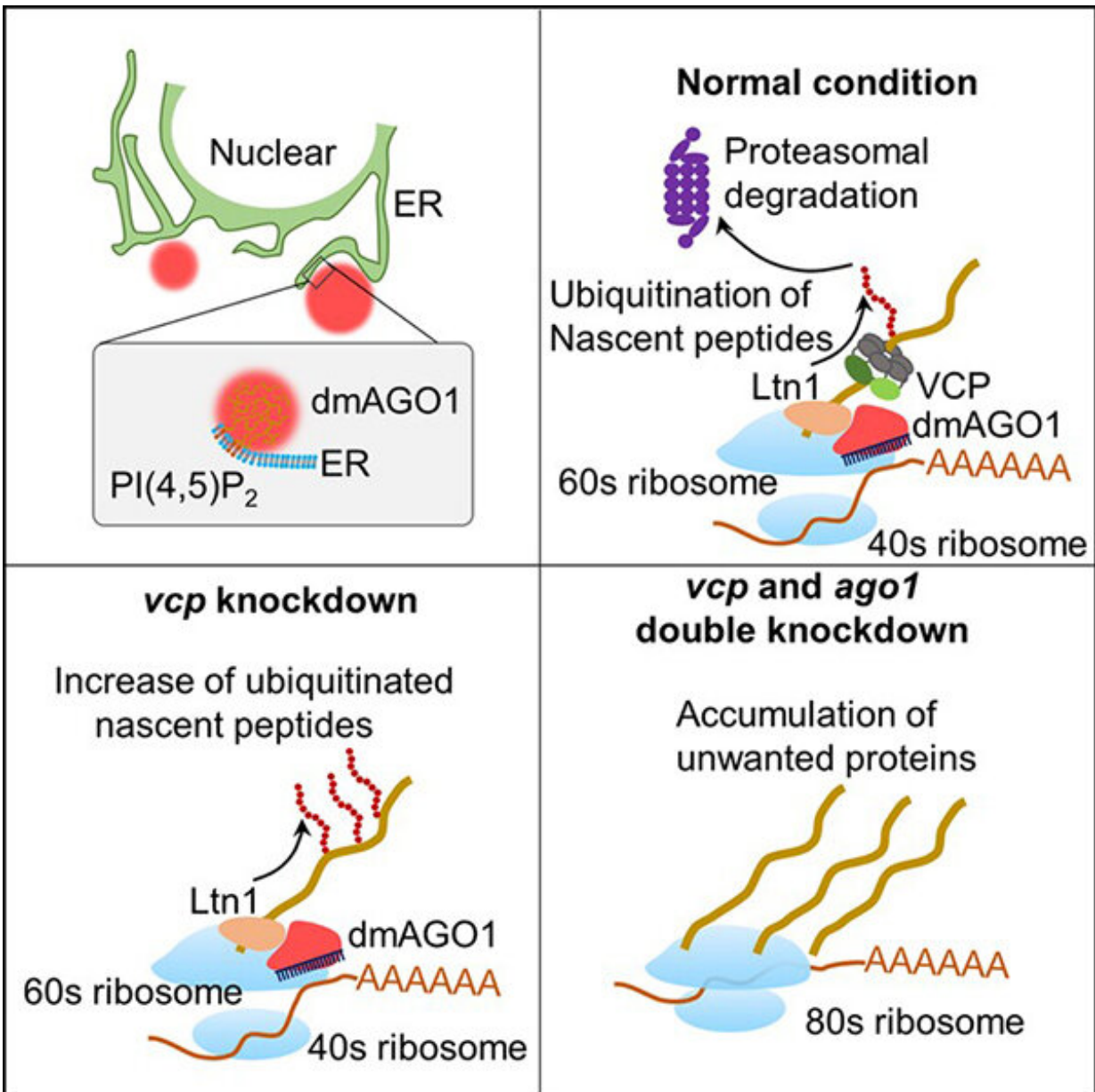


# Researchers reveal novel role of Argonaute proteins in regulating protein quality control

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The mechanism of lipid-mediated phase separation of AGO proteins on the ER in regulating nascent-peptide ubiquitination. Credit: Chen lab

The miRNA-mediated gene silencing and the ubiquitin-mediated protein quality control represent two fundamental mechanisms for controlling gene expression. However, little is known about how these processes are coupled to regulate gene expression.

In a recent issue of *Molecular Cell*, researchers led by Sun Qinmiao from the Institute of Zoology of the Chinese Academy of Sciences and Chen Dahua from Yunnan University discovered that Argonaute (AGO) proteins on the [endoplasmic reticulum](#) (ER) play a novel role in regulating protein quality control via [lipid](#)-mediated phase separation, substantially coupling post-transcriptional gene silencing and protein quality control processes to ensure efficient gene silencing.

AGOs are well-known to silence target gene expression by interacting with miRNAs and involved in regulating a wide variety of biological processes. In addition to their cytoplasmic localization, AGOs have also been reported to associate with membrane-bound organelles including ER. However, the functional role of AGO proteins' association with the ER membrane and how this association is regulated have been unknown.

In this study, the researchers discovered a conserved lipid-binding motif in the N domain of AGO proteins that specifically interacts with PI(4, 5)P<sub>2</sub> and the AGO-PI(4, 5)P<sub>2</sub> interaction enhanced the [phase separation](#) of AGOs on the ER.

Moreover, they found that the ER-localized AGO condensates recruits Ltn1 to catalyze nascent-peptide ubiquitination, subsequently leading to degradation of the unwanted protein products.

These findings suggest that AGOs on the ER can couple two fundamental cellular processes, post-transcriptional gene silencing and protein quality control, to ensure proper [gene expression](#).

Human AGO2 overexpression is related to tumorigenesis and cancer aggressiveness and its lipid-binding motif contains two cancer-related mutations, so it will be of great interest to investigate whether the lipid-mediated membrane function of human AGO2 is related to cancer development in the future, according to the researchers.

**More information:** Yajie Gao et al, Lipid-mediated phase separation of AGO proteins on the ER controls nascent-peptide ubiquitination, *Molecular Cell* (2022). [DOI: 10.1016/j.molcel.2022.02.035](https://doi.org/10.1016/j.molcel.2022.02.035)

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