

Researchers decipher an alternative mechanism of intracellular protein trafficking

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The new scientific research describes existing alternative mechanisms to the traditional export model of synthesized proteins in the endoplasmic reticulum.

Research, published on the cover of the journal *Traffic*, describes

existing alternative mechanisms to the traditional export model of newly synthesized membrane and secretory proteins from the endoplasmic reticulum (ER). The article is signed by an international group composed of Professor Pedro Moral, head of the Consolidated Research Group on Human Population Biology of the Anthropology Unit at the Faculty of Biology of the UB, affiliated centre with the campus of International excellence BKC, and Meritxell Cutrona, collaborator at the Unit and member of Consorzio Mario Negri Sud and Gabriele d'Annunzio University Foundation (Italy).

This study is mainly focused on mechanisms of [membrane trafficking](#) and export of proteins from the ER, and analyses the functional organisation of the early [secretory pathway](#) (ER-to-Golgi boundary). By the secretory pathway, cells coordinate the movement of proteins toward the [plasma membrane](#), the extracellular environment and other membrane compartments within the cell. The early secretory pathway comprises membrane-enclosed organelles -or secretory stations- including the [endoplasmic reticulum](#), the intermediate compartment and the [Golgi apparatus](#), as well as membrane carriers which travel in between them.

Intense membrane trafficking within the cell

According to Meritxell Cutrona, the first author of the article, "the discovery of the secretory process revealed the importance of understanding the [molecular mechanisms](#) and regulating factors of membrane —and protein— trafficking within the cell". The vesicular transport hypothesis states that the transfer of cargo proteins between organelles of the secretory pathway is mediated by shuttling transport vesicles. Accordingly, vesicles bud from a donor compartment -allowing the selective incorporation and sorting of cargo- and subsequently are targeted to a specific acceptor compartment, into which they fuse and unload their cargo.

A series of molecular machineries regulate transport steps along the secretory pathway. According to the classical view of the protein secretion process, the biogenesis of transport vesicles from the endoplasmic reticulum membranes is exclusively mediated by the function of the multiprotein complex COPII, therefore providing the main export mechanism which ensures the access to the secretory pathway of proteins synthesized in the endoplasmic reticulum.

Meritxell Cutrona remarks that "some observations provide exceptions to the predictions of the classical model, which may question the generality of the unique requirement of the COPII function to ensure the export of cargo proteins from the endoplasmic reticulum". These exceptions fall into the category of the "COPII-bypass", which is included in unconventional or non-classical paths of protein secretion. The phenomenon of COPII bypass was initially observed in mutant strains of yeast *S. cerevisiae* defective for the function of specific COPII subunits, suggesting that COPII function could be unnecessary at least for the ER exit of a limited number of cargo proteins. Interestingly, COPII bypass has been recently observed in mammalian cells but the mechanisms regulating alternative non-canonical paths are still unknown.

An alternative to the classical COPII-based model of ER export of proteins

In the study, authors abrogated COPII function (to ablate the canonical framework of ER export of cargo proteins) in order to characterise unconventional secretory routes associated with the bypass of the COPII function. This study presents an innovative approach as the authors used small interfering RNA-mediated depletion of Sar1A and Sar1B in mammalian cells. The Sar1 GTPase plays a key function by coordinating the assembly of COPII at specific sites of the ER membrane. Under depletion of these two mammalian forms of Sar1 the cells fail to

organize transitional elements that coordinate classical ER-to-Golgi protein transfer. "This innovative methodology —Pedro Moral states— has provided one of the most important evidences to prove the existence of alternative mechanisms to the classical COPII-dependent vesicular of biosynthetic trafficking in mammalian cells".

The research reveals a strategy that may be useful to identify general regulators involved in alternative transport mechanisms, characterise functional and morphological aspects of alternative routes, and establish potential users among synthetized proteins in the endoplasmic reticulum. Meritxell Cutrona concludes that "the study also shows a new transport regulation level when COPII function is inhibited by Sar1 depletion. The existence of alternative routes —and not a single one— for synthetized proteins in endoplasmic reticulum will open new research lines on cell biology and certain pathologies related to protein retention in the endoplasmic reticulum (for example, cystic fibrosis)".

More information: Cutrona, M. et al. Silencing of Mammalian Sar1 Isoforms Reveals COPII-Independent Protein Sorting and Transport, *Traffic*.

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