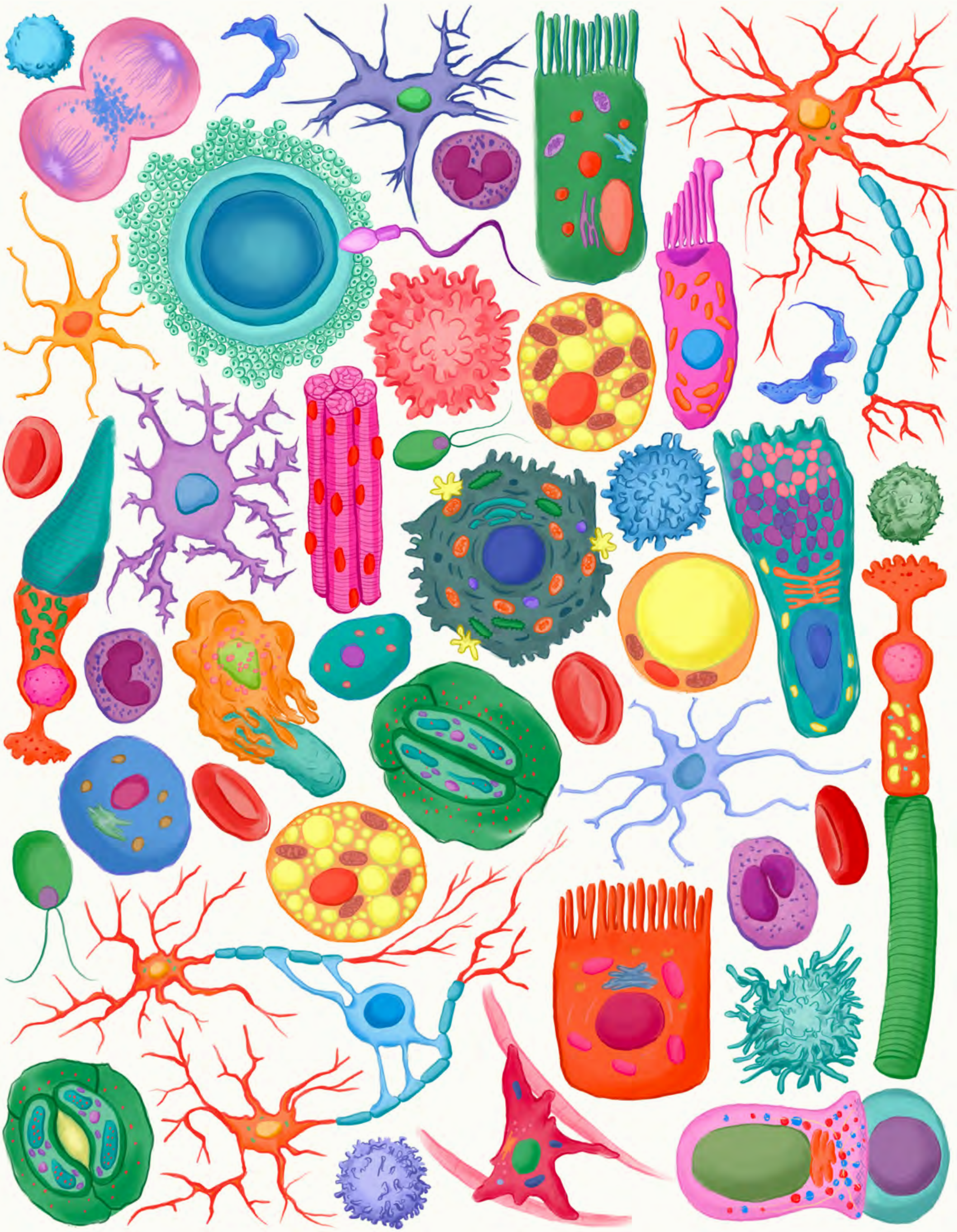

THE YEAR IN CELL BIOLOGY 2025

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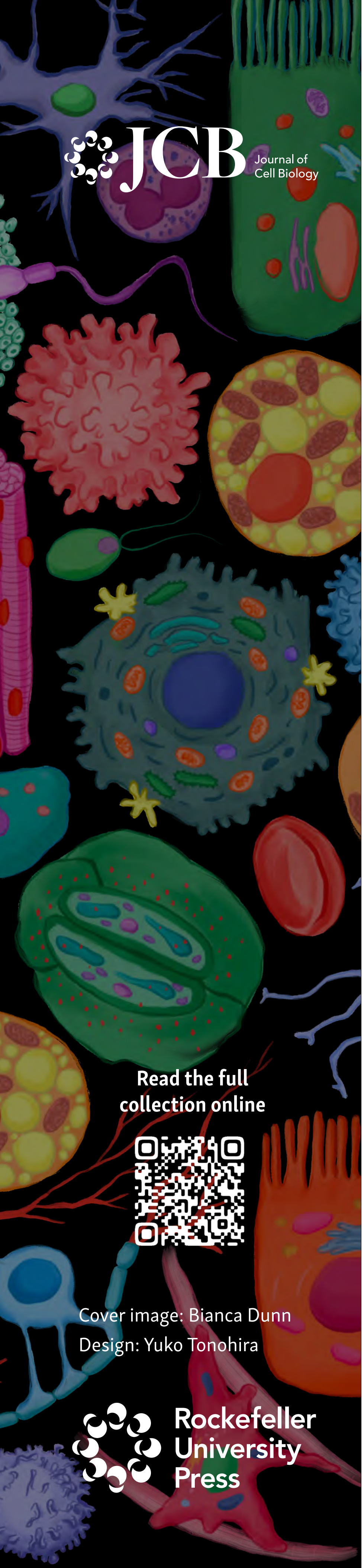

THE YEAR IN CELL BIOLOGY 2025

The editorial team at the *Journal of Cell Biology* (*JCB*) is excited to present a collection of the year's most impactful papers, which have garnered exceptional interest from our readership.

The collection features new advances in plasma membrane repair, autophagy, protein homeostasis, and organelle-dependent cell signaling. It explores mechanisms underlying the phagocytic fate of epithelial cells as well as the interplay between lysosomal exocytosis and focal adhesions. It presents a new meiosis-specific organelle and introduces valuable resources such as a proteome-wide yeast degron library. Additional highlights include discoveries on how sphingolipid metabolism regulates stem cell homeostasis and how mitochondrial dynamics affect astrocyte morphogenesis. Find more Year in Cell Biology articles and selections beyond what's covered in this magazine at rupress.org/jcb/collections.

JCB is proud to continue publishing high-quality research. We are grateful that scientists regard our journal as a leading venue for their groundbreaking discoveries as well as for our reviewers' and readers' support and enthusiasm. We reflect on a year of cutting-edge findings spanning the diverse spectrum of cell biology and look forward to a new year of transformative research ahead.

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Secretion of microvesicles during membrane repair

Microvesicles (MVs) are membrane-enclosed, plasma membrane–derived particles released by cells from all branches of life. MVs have utility as disease biomarkers and may participate in intercellular communication; however, physiological processes that induce their secretion are not known.

Here, we isolate and characterize annexin-containing MVs and show that these vesicles are secreted in response to the calcium influx caused by membrane damage. The annexins in these vesicles are cleaved by calpains. After plasma membrane injury, cytoplasmic calcium-bound annexins are rapidly recruited to the plasma membrane and form a scab-like structure at the lesion. In a second phase, recruited annexins are cleaved by calpains-1/2, disabling membrane scabbing. Cleavage promotes annexin secretion within MVs.

Our data support a new model of plasma membrane repair, where calpains relax annexin-membrane aggregates in the lesion repair scab, allowing secretion of damaged membrane and annexins as MVs. We anticipate that cells experiencing plasma membrane damage, including muscle and metastatic cancer cells, secrete these MVs at elevated levels.

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ORIGINAL PAPER

Williams, J.K., J.M. Ngo, A. Murugupandiyan, D.E. Croall, H.C. Hartzell, and R. Schekman. 2025. Calpains orchestrate secretion of annexin-containing microvesicles during membrane repair. *J. Cell Biol.* 224 (7): e202408159. https://doi.org/10.1083/jcb.202408159

Identification of organelle-specific autophagy regulators

Autophagy is a conserved degradative process that promotes cellular homeostasis under stress conditions. Under nutrient starvation, autophagy is nonselective, promoting indiscriminate breakdown of cytosolic components. Conversely, selective autophagy is responsible for the specific turnover of damaged organelles. We hypothesized that selective autophagy may be regulated by signaling pathways distinct from those controlling starvation-induced autophagy, thereby promoting organelle turnover.

To address this question, we conducted kinome-wide CRISPR screens to identify distinct signaling pathways responsible for the regulation of basal autophagy, starvation-induced autophagy, and two types of selective autophagy: ER-phagy and pexophagy. These parallel screens identified both known and novel autophagy regulators, some common to all conditions and others specific to selective autophagy. More specifically, CDK11A and NME3 were further characterized to be selective ER-phagy regulators. Meanwhile, PAN3 and CDC42BPG were identified as an activator and inhibitor of pexophagy, respectively.

Collectively, these datasets provide the first comparative description of the kinase signaling that defines the regulation of selective autophagy and bulk autophagy.

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ORIGINAL PAPER

Losier, T.T., K.E. King, M.W.C. Rousseaux, and R.C. Russell. 2025. Identification of organelle-specific autophagy regulators from tandem CRISPR screens. *J. Cell Biol.* 224 (10): e202405138. https://doi.org/10.1083/jcb.202405138

A signaling pathway linking lysosome perturbation to LRRK2 activation

Mutations that increase LRRK2 kinase activity have been linked to Parkinson's disease and Crohn's disease. LRRK2 is also activated by lysosome damage. However, the endogenous cellular mechanisms that control LRRK2 kinase activity are not well understood.

In this study, we identify signaling through stimulator of interferon genes (STING) as an activator of LRRK2 via the conjugation of ATG8 to single membranes (CASM) pathway. We furthermore establish that multiple chemical stimuli that perturb lysosomal homeostasis also converge on CASM to activate LRRK2. Although CASM results in the lipidation of multiple ATG8 protein family members, we establish that LRRK2 lysosome recruitment and kinase activation are highly dependent on interactions with the GABARAP member of this family.

Collectively, these results define a pathway that integrates multiple stimuli at lysosomes to control the kinase activity of LRRK2. Aberrant activation of LRRK2 via this pathway may be of relevance in both Parkinson's and Crohn's diseases.

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ORIGINAL PAPER

Bentley-DeSousa, A., A. Roczniak-Ferguson, and S.M. Ferguson. 2025. A STING–CASM–GABARAP pathway activates LRRK2 at lysosomes. *J. Cell Biol.* 224 (2): e202310150. https://doi.org/10.1083/jcb.202310150

The architecture of cytoplasmic ribosomes on mitochondrial membranes

Most of the mitochondria proteome is nuclear encoded, synthesized by cytoplasmic ribosomes, and targeted to the mitochondria posttranslationally. However, a subset of mitochondrial-targeted proteins is imported co-translationally, although the molecular mechanisms governing this process remain unclear.

We employ cellular cryo-electron tomography to visualize interactions between cytoplasmic ribosomes and mitochondria in *Saccharomyces cerevisiae*. We use surface morphometrics tools to identify a subset of ribosomes optimally oriented on mitochondrial membranes for protein import. This allows us to establish the first subtomogram average structure of a cytoplasmic ribosome at the mitochondrial surface in the native cellular context, which showed three distinct connections with the outer mitochondrial membrane surrounding the peptide exit tunnel. Further, this analysis demonstrated that cytoplasmic ribosomes primed for mitochondrial protein import cluster on the outer mitochondrial membrane at sites of local constrictions of the outer and inner mitochondrial membranes.

Overall, our study reveals the architecture and the spatial organization of cytoplasmic ribosomes at the mitochondrial surface, providing a native cellular context to define the mechanisms that mediate efficient mitochondrial co-translational protein import.

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ORIGINAL PAPER

Chang, Y.-T., B.A. Barad, J. Hamid, H. Rahmani, B.M. Zid, and D.A. Grotjahn. 2025. Cytoplasmic ribosomes on mitochondria alter the local membrane environment for protein import. *J. Cell Biol.* 224 (4): e202407110. https://doi.org/10.1083/jcb.202407110

Ecdysone promotes nonprofessional phagocytic cell fate

Acquisition of nonprofessional phagocytic cell fate plays an important role in sculpting functional metazoan organs and maintaining overall tissue homeostasis. Though physiologically highly relevant, how the normal epithelial cells acquire phagocytic fate is still mostly unclear.

We have employed the *Drosophila* ovary model to demonstrate that classical ecdysone signaling in the somatic epithelial follicle cells (AFCs) aids the removal of germline nurse cells (NCs) in late oogenesis. Our live-cell imaging data reveal a novel phenomenon wherein collective behavior of 4–5 AFCs is required for clearing a single NC. By employing classical genetics, molecular biology, and yeast one-hybrid assay, we demonstrate that ecdysone modulates the phagocytic disposition of AFCs at two levels. It regulates the epithelial–mesenchymal transition of the AFCs through Serpent and modulates the phagocytic behavior of the AFCs through Croquemort and Draper.

Our data provide unprecedented novel molecular insights into how ecdysone signaling reprograms AFCs toward a phagocytic fate.

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ORIGINAL PAPER

Ghosh, G., D. Das, A. Nandi, S. De, S.N. Gangappa, and M. Prasad. 2025. Ecdysone regulates phagocytic cell fate of epithelial cells in developing *Drosophila* eggs. *J. Cell Biol.* 224 (8): e202411073. https://doi.org/10.1083/jcb.202411073

A proteome-wide yeast degron library for “on-demand” protein depletion

Genome-wide collections of yeast strains, known as libraries, revolutionized the way systematic studies are carried out. Specifically, libraries that involve a cellular perturbation, such as the deletion collection, have facilitated key biological discoveries. However, short-term rewiring and long-term accumulation of suppressor mutations often obscure the functional consequences of such perturbations.

We present the AID library, which supplies “on demand” protein depletion to overcome these limitations. Here, each protein is tagged with a green fluorescent protein (GFP) and an auxin-inducible degron (AID), enabling rapid protein depletion that can be quantified systematically using the GFP element.

We characterized the degradation response of all strains and demonstrated its utility by revisiting seminal yeast screens for genes involved in cell cycle progression as well as mitochondrial distribution and morphology. In addition to recapitulating known phenotypes, we also uncovered proteins with previously unrecognized roles in these central processes.

Hence, our tool expands our knowledge of cellular biology and physiology by enabling access to phenotypes that are central to cellular physiology and therefore rapidly equilibrated.

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Photo credit: Ohad Herches, Weizmann Institute of Science Photography Department

ORIGINAL PAPER

Valenti, R., Y. David, D. Edilbi, B. Dubreuil, A. Boshnakovska, Y. Asraf, T.-M. Salame, E. Sass, P. Rehling, and M. Schuldiner. 2025. A proteome-wide yeast degron collection for the dynamic study of protein function. *J. Cell Biol.* 224 (2): e202409050. https://doi.org/10.1083/jcb.202409050

JCB Journal of Cell Biology

Sphingolipids control the hair follicle stem cell compartment

Sphingolipids serve as building blocks of membranes to ensure subcellular compartmentalization and facilitate intercellular communication. How cell type–specific lipid compositions are achieved and what their functional significance in tissue morphogenesis and maintenance is has remained unclear.

Here, we identify a stem cell–specific role for ceramide synthase 4 (CerS4) in orchestrating fate decisions in skin epidermis. Deletion of CerS4 prevents the proper development of the adult hair follicle bulge stem cell (HFSC) compartment due to altered differentiation trajectories. Mechanistically, HFSC differentiation defects arise from an imbalance of key ceramides and their derivate sphingolipids, resulting in hyperactivation of noncanonical Wnt signaling. This impaired HFSC compartment establishment leads to disruption of hair follicle architecture and skin barrier function, ultimately triggering a T helper cell 2–dominated immune infiltration resembling human atopic dermatitis.

This work uncovers a fundamental role for a cell state–specific sphingolipid profile in stem cell homeostasis and in maintaining an intact skin barrier.

ORIGINAL PAPER

Peters, F., W. Höfs, H. Lee, S. Brodesser, K. Kruse, H.C.A. Drexler, J. Hu, V.K. Raker, D. Lukas, E. von Stebut, M. Krönke, C.M. Niessen, and S.A. Wickström. 2025. Sphingolipid metabolism orchestrates establishment of the hair follicle stem cell compartment. *J. Cell Biol.* 224 (4): e202403083. https://doi.org/10.1083/jcb.202403083

RESEARCHER DETAILS

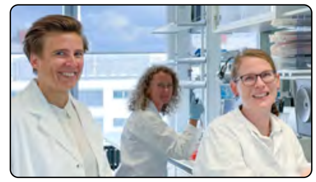

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Photo credit: MPI-MBM

Drp1 controls astrocyte morphology and organization

Dysfunctional mitochondrial dynamics are a hallmark of devastating neurodevelopmental disorders such as childhood refractory epilepsy. However, the role of glial mitochondria in proper brain development is not well understood.

We show that astrocyte mitochondria undergo extensive fission while populating astrocyte distal branches during postnatal cortical development. Loss of mitochondrial fission regulator, dynamin-related protein 1 (Drp1), decreases mitochondrial localization to distal astrocyte processes, and this mitochondrial mislocalization reduces astrocyte morphological complexity. Functionally, astrocyte-specific conditional deletion of Drp1 induces astrocyte reactivity and disrupts astrocyte organization in the cortex. These morphological and organizational deficits are accompanied by loss of perisynaptic astrocyte process proteins such as gap junction protein connexin 43.

These findings uncover a crucial role for mitochondrial fission in coordinating astrocytic morphogenesis and organization, revealing the regulation of astrocytic mitochondrial dynamics as a critical step in neurodevelopment.

ORIGINAL PAPER

Rodriguez Salazar, M.P., S. Kolanukuduru, V. Ramirez, B. Lyu, G. Manigault, G. Sejourne, H. Sesaki, G. Yu, and C. Eroglu. 2025. Mitochondrial fission controls astrocyte morphogenesis and organization in the cortex. *J. Cell Biol.* 224 (10): e202410130. https://doi.org/10.1083/jcb.202410130

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Focal adhesion maturation promotes lysosomal exocytosis

Many cancer cells exhibit increased amounts of paucimannose glycans, which are truncated *N*-glycan structures rarely found in mammals. Paucimannosidic proteins are proposedly generated within lysosomes and exposed on the cell surface through a yet uncertain mechanism.

In this study, we revealed that paucimannosidic proteins are produced by lysosomal glycosidases and secreted via lysosomal exocytosis. Interestingly, lysosomal exocytosis preferentially occurred in the vicinity of focal adhesions, protein complexes connecting the actin cytoskeleton to the extracellular matrix. Through genome-wide knockout screening, we identified that MYO18B, an actin crosslinker, is required for focal adhesion maturation, facilitating lysosomal exocytosis and the release of paucimannosidic lysosomal proteins to the extracellular milieu. Moreover, a mechanosensitive cation channel PIEZO1 locally activated at focal adhesions imports Ca^{2+} necessary for lysosome–plasma membrane fusion.

Collectively, our study unveiled an intimate relationship between lysosomal exocytosis and focal adhesion, shedding light on the unexpected interplay between lysosomal activities and cellular mechanosensing.

ORIGINAL PAPER

Ren, W.-W., R. Kawahara, K.G.N. Suzuki, P. Dipta, G. Yang, M. Thaysen-Andersen, and M. Fujita. 2025. MYO18B promotes lysosomal exocytosis by facilitating focal adhesion maturation. *J. Cell Biol.* 224 (3): e202407068. https://doi.org/10.1083/jcb.202407068

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An interkinetic envelope is assembled during oocyte meiosis

At the end of cell division, the nuclear envelope reassembles around the decondensing chromosomes. Female meiosis culminates in two consecutive cell divisions of the oocyte, meiosis I and II, which are separated by a brief transition phase known as interkinesis. Due to the absence of chromosome decondensation and the suppression of genome replication during interkinesis, it has been widely assumed that the nuclear envelope does not reassemble between meiosis I and II.

By analyzing interkinesis in *C. elegans* oocytes, we instead show that an atypical structure made of two lipid bilayers, which we termed the interkinetic envelope, surrounds the surface of the segregating chromosomes. The interkinetic envelope shares common features with the nuclear envelope but also exhibits specific characteristics that distinguish it, including its lack of continuity with the endoplasmic reticulum, unique protein composition, assembly mechanism, and function in chromosome segregation.

These distinct attributes collectively define the interkinetic envelope as a unique and specialized structure that has been previously overlooked.

ORIGINAL PAPER

El Mossadeq, L., L. Bellutti, R. Le Borgne, J.C. Canman, L. Pintard, J.-M. Verbavatz, P. Askjaer, and J. Dumont. 2025. An interkinetic envelope surrounds chromosomes between meiosis I and II in *C. elegans* oocytes. *J. Cell Biol.* 224 (3): e202403125. https://doi.org/10.1083/jcb.202403125

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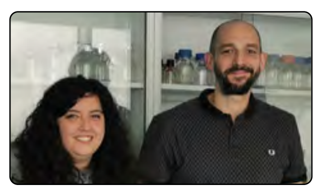

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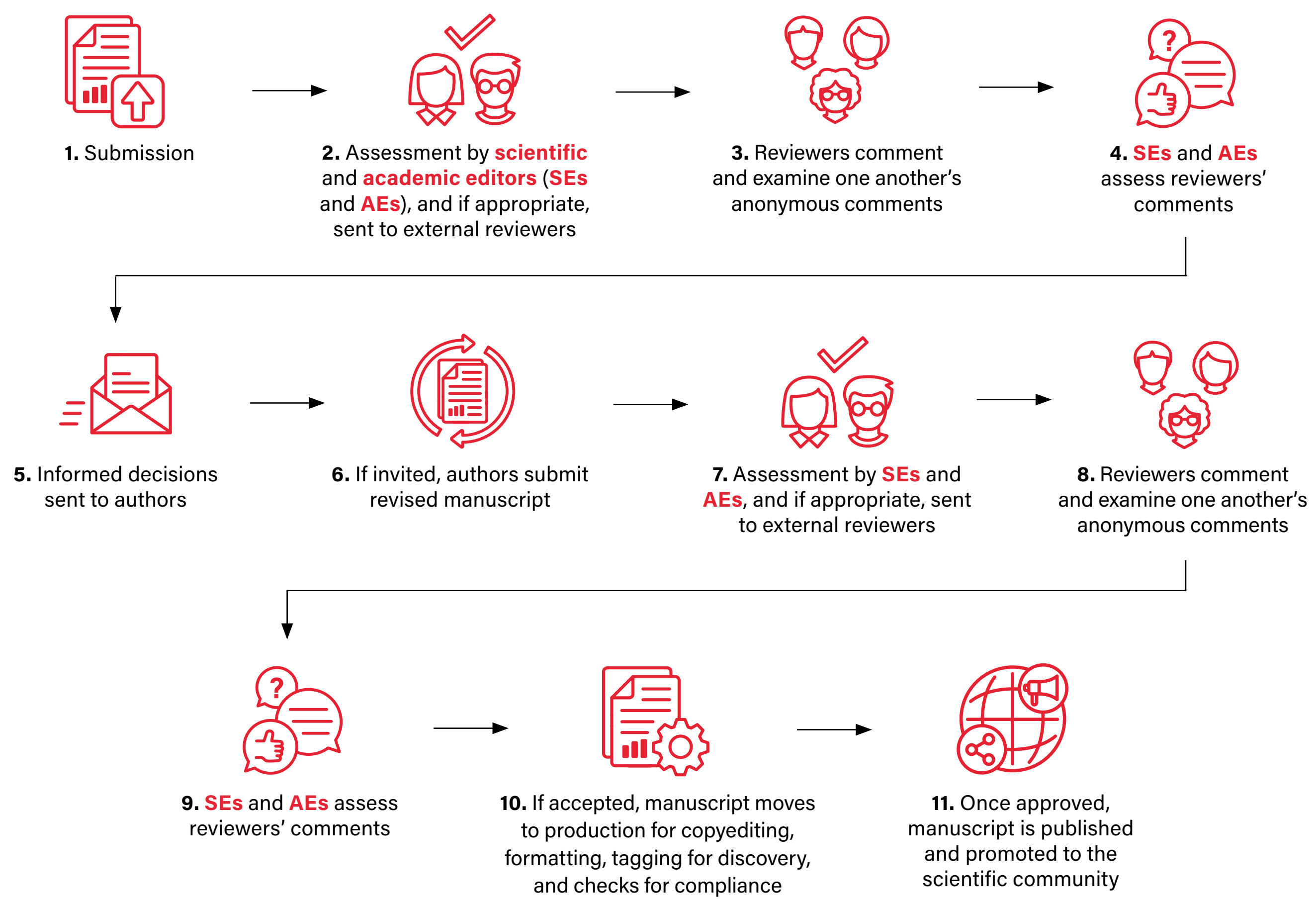

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