2-induced secretion of exosomes is a protective mechanism against ferroptotic cell death.

Exosomes derived from GPX-inhibitor-treated, ferroptosis-resistant cells contained ferritin — an important iron-storing protein. Furthermore, prominin 2 levels were anti-correlated with cellular levels of free iron upon ferroptosis induction. This led the authors to conclude that exosomes are a route for expelling iron out of cells exposed to ferroptotic stimuli, thereby protecting them from ferroptotic cell death.

Moving forwards, it would be interesting to study the prominin 2-driven exosomal expulsion of iron in more detail; this could open up new therapeutic opportunities to regulate ferroptotic cell death in human pathology.

Paulina Strzyz

ORIGINAL ARTICLE Brown, C. W. et al. Prominin2 drives ferroptosis resistance by stimulating multivesicular body/exosome-mediated iron export. *Dev. Cell* <https://doi.org/10.1016/j.devcel.2019.10.007> (2019)

RELATED ARTICLE van Niel, G., D'Angelo, G. & Raposo, G. Shedding light on the cell biology of extracellular vesicles. *Nat. Rev. Mol. Cell Biol.* **19**, 213–228 (2018)

that CDK1 phosphorylates these regulatory proteins instead of mTORC1 during mitosis.

To confirm that this effect occurs in actively dividing cells, the authors treated cells with RO-3306 and allowed them to continue through the cell cycle in drug-free medium. Phosphorylation of autophagy regulators was observed as the cells entered mitosis, an effect resistant to inhibition of mTORC1.

Using purified GST fusion proteins containing regions of autophagy regulators usually phosphorylated by mTORC1, the authors showed that cyclin B1–CDK1 complexes were able to phosphorylate ATG13, ATG14, TFEB and ULK1 directly in vitro at the same sites as mTORC1.

Thus, by switching from mTORC1- to CDK1-mediated phosphorylation of autophagy regulators, cells appear to protect their nuclear contents during cell division by uncoupling the regulation of autophagy from nutrient availability.

Joseph Willson

ORIGINAL ARTICLE Odle, R. I. et al. An mTORC1-to-CDK1 switch maintains autophagy suppression during mitosis. *Mol. Cell* <https://doi.org/10.1016/j.molcel.2019.10.016> (2019)

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TRANSCRIPTION

Integrator of stress cues

Precise regulation of RNA polymerase II (Pol II) is necessary for maintaining cellular homeostasis. The fate of a transcript can be determined by several processes after Pol II initiates transcription. The Integrator complex has a role in 3'-end formation of small nuclear RNAs (snRNAs) and is known to interact with transcribing Pol II. A new study now shows that Integrator also fine-tunes mRNA production.

In search of regulators of transcription elongation, Tatomer et al. performed an RNAi screen in fruit fly cells employing an eGFP gene under the control of the metallothionein A (*MtnA*) gene promoter, which is activated by high copper levels (the protein chelates metal ions). Because the reporter transcript is unspliced and non-polyadenylated, changes in eGFP expression preferentially uncover transcription (and translation) regulators.

Automated microscopy and image analysis identified 232 factors required for reporter expression in cells subjected to copper stress. Unexpectedly, nearly all Integrator subunits scored as potent negative regulators of both the reporter gene and the endogenous *MtnA* gene. This function required the RNA endonuclease activity of Integrator complex subunit 11 (IntS11).

Among positive transcription regulators identified in the screen were several subunits of the nuclear RNA exosome, such as Mtr4, which catalyses 3'–5' degradation of nuclear transcripts. Intriguingly, Mtr4 depletion not only reduced the levels of full-length *MtnA* mRNA, but also increased the production of shorter *MtnA* RNAs. These short RNAs were capped, shared the same transcription start site with full-length *MtnA* and were lost upon co-depletion of Mtr4 and Integrator.

Given that Integrator and the nuclear exosome interact directly, the authors suggest that Integrator cleaves nascent *MtnA* mRNAs, which are in turn degraded by the exosome, thereby inducing premature transcription termination. This role is mechanistically related to the cleavage of nascent snRNAs, suggesting that Integrator function at snRNAs has been repurposed to regulate protein-coding genes.

Next, the authors identified 409 genes upregulated in IntS9-depleted and copper-treated cells. Many of the genes are involved in cellular responses to stimuli, indicating that Integrator has a wide role in triggering mRNA transcription termination. Integrator was recruited to the 5'-end of all tested loci and generated short RNAs, which were cleared by the exosome. The discrete size of Integrator-dependent short RNAs does not seem to depend on mRNA sequence, but possibly on nucleosome positioning or Pol II pausing or stalling.

In summary, Integrator fine-tunes mRNA levels in response to cellular stress. By cleaving nascent transcripts and transferring them to the nuclear exosome, Integrator attenuates productive transcription elongation, thereby providing an additional layer of Pol II regulation.

Marzia Munafò

ORIGINAL ARTICLE Tatomer, D. C. et al. The Integrator complex cleaves nascent mRNAs to attenuate transcription. *Genes Dev.* **33**, 1525–1538 (2019)

RELATED ARTICLE Chen, F. X. et al. Born to run: control of transcription elongation by RNA polymerase II. *Nat. Rev. Mol. Cell Biol.* **19**, 464–478 (2018)

“secretion of exosomes is a protective mechanism against ferroptotic cell death”