MEMBRANE TRAFFICKING

Lysosomal disorder boosts STING

Nature https://www.nature.com/articles/s41586-021-03762-2 (2021)

To avoid immunopathology, cells dampen inflammation by eliminating signalling components. STING, which acts downstream of the DNA sensor cyclic GMP–AMP synthase (cGAS), traffics to lysosomes for degradation. Yan and colleagues report that the lysosomal membrane protein Niemann–Pick type C1 (NPC1) recruits STING to lysosomes. Lack of NPC1 induces STING signalling independently of cGAS, which contributes to neuropathology in mice.

NPC1 mutations underlie Niemann–Pick disease type C1, a lipid storage disorder characterized by neurodegeneration. NPC1 mediates cholesterol egress from endolysosomes; NPC1-deficient patient cells accumulate lipids in lysosomes and activate ER-to-Golgi translocation of the SREBP–SCAP complex to regulate lipogenesis and cholesterol metabolism. By analysing organelle-specific STING interactomes, Yan and colleagues found that STING associates with NPC1. They characterized immune signalling and disease phenotypes in cellular and rodent models deficient in *Npc1*, *Npc1* and *Sting*, or *Npc1* and *Cgas*. Absence of NPC1 activated STING, promoting neuroinflammation and neuropathology independently of cGAS. Mechanistically, NPC1 deficiency triggered STING responses through enhanced ER-to-Golgi trafficking of the SREBP–STING complex and decreased lysosomal degradation of STING. This study suggests that targeting STING signalling may be relevant for the treatment of Niemann–Pick disease type C. *MC*

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CANCER

TRIM8 in Ewing sarcoma

Cancer Cell https://doi.org/10.1016/j.ccell.2021.07.003 (2021)

EWS/FLI is a chimeric fusion oncogene that drives tumour formation and progression in Ewing sarcoma. Using a CRISPR–Cas9 screening approach, Stegmaier and colleagues show that the E3 ligase TRIM8 selectively regulates EWS/FLI ubiquitination, degradation and function in Ewing sarcoma.

Specifically, after performing multiple independent CRISPR–Cas9 screens in 293T cells and across distinct cancer cell lines, the authors identified TRIM8 as a selective genetic dependency in Ewing sarcoma. They then found reduced tumour growth in TRIM8-silenced xenograft models, and showed that this could be at least partially attributed to increased EWS/FLI expression. The authors went on to study the effect of oncogene overdose using inducible overexpression of EWS/FLI, and observed enhanced apoptosis and reduced growth in Ewing sarcoma cells. EWS/FLI overexpression or TRIM8 inhibition was associated with increased sensitivity to PARP inhibitors. Further mechanistic analysis showed that TRIM8 selectively interacted with and ubiquitinated EWS/FLI in Ewing sarcoma cells, and that this required C1 and C5 domains of EWS/FLI. Lastly, the authors identified K144 and K334 as important lysine residues on EWS/FLI for TRIM8-mediated degradation.

Overall, this study uncovers an E3 ligase that safeguards the deleterious effect of EWS/FLI overdose, providing another potential therapeutic approach to target Ewing sarcoma. *ZW*

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ORGANOIDS

Modelling SARS-CoV-2 CNS infection

Nature Medicine https://doi.org/10.1038/s41591-021-01443-1 (2021)

Respiratory symptoms of SARS-CoV-2 infections are well studied, but the origins of associated neurological complications remain less clear. Previous reports on brain organoids concluded that most neural cells are not infected by SARS-CoV-2. However, choroid plexus epithelial cells, immune cells and neurovascular cells in the brain are vulnerable. Gleeson and colleagues now show that the vascular cells, or pericytes, perform important functions in the central nervous system (CNS), maintain the blood–brain barrier, regulate inflammatory responses and interact with neighbouring neurons and astrocytes.

Having shown that human pericyte-like cells (PLCs) could be infected with SARS-CoV-2, the authors integrated them into cortical organoids. Under homeostasis, PLCs maintained their morphology and functions as expected and promoted maturation of astrocytes. When exposed to SARS-CoV-2, only the organoids that contained PLCs were prone to infection, and normal cortical organoids did not show viral replication. The astrocyte population became vulnerable to infection by the presence of PLCs and increasingly underwent apoptosis or activated inflammatory signalling.

Together, the authors identify PLCs as an interesting target and promoter of SARS-CoV-2 invasion in the CNS, which might also enable its spread to other cell types. *CW*

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Melina Casadio, Zhe Wang, Jie Wang and Christine Weber

PHASE SEPARATION

Supporting nucleolar liquidity

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The nucleolus is a multilayered liquid condensate for ribosome biogenesis, but how its liquid property is maintained is unknown. Chen and colleagues now show that the nucleolar long noncoding RNA (lncRNA) SLERT supports the liquidity of the dense fibrillar component (DFC) in the nucleolus for efficient rDNA transcription.

The authors previously reported that SLERT reverses the negative effect of the RNA helicase DDX21 on rDNA transcription. They now find that after binding to SLERT, DDX21 adopts a closed conformation owing to increased intramolecular interactions, thereby forming a loose shell that coats the DFC. This confers the DFC with sufficient size and liquidity that are essential for polymerase I (Pol I) processivity. In addition, the authors show that DDX21 is able to approach and wrap rDNA to block Pol I processivity; however, this ability is repressed by a SLERT-induced conformational change. Notably, they find that each FC and DFC unit contains 1,000-fold fewer SLERT molecules than DDX21. Given the chaperone-like property of SLERT to continuously induce conformational changes of DDX21 in vitro, they propose that SLERT may act as an RNA chaperone to control DDX21 conformation in a substoichiometric manner.

Together, the study reports an interesting mechanism by which the lncRNA SLERT controls nucleolar biophysical properties by altering DDX21 conformation. *JW*

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