JEM Journal of Experimental Medicine

INSIGHTS

Taking the STING out of neurodegenerative disease

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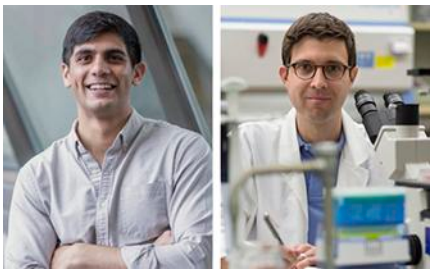
New work from Yang et al. (https://doi.org/10.1084/jem.20242296) provides an exhaustive study of a novel mouse model of NGLY1 deficiency, a devastating neurological disease, and implicates the cGAS-STING pathway in mediating key disease features which can be rescued using an orally administered STING antagonist.

NGLY1 deficiency is a rare, congenital disease with no approved treatments to slow or stop progression. Affected individuals experience a shortened lifespan along with a host of devastating neurological symptoms including global developmental delay, muscle weakness, ataxia, and polyneuropathies (Tong et al., 2023). This disorder is attributed to loss-of-function mutations in the *NGLY1* gene, encoding N-glycanase 1, an enzyme that plays a role in the quality control and proper folding of newly synthesized proteins that have undergone N-glycosylation. Previous in vitro work on NGLY1-deficient human and mouse cells has suggested that errors in mitophagy, the process by which damaged mitochondria are recycled by the cell, and subsequent activation of the Cyclic GMP-AMP Synthase - Stimulator of Interferon Genes (cGAS-STING) pathway by mitochondrial DNA contribute to cellular dysfunction (Yang et al., 2018; Han et al., 2020; Kong et al., 2018). Yet, how NGLY1 deficiency impacts in vivo neurobiology and leads to neurological disease has remained poorly understood.

To better understand the pathophysiology of disease, the authors set about constructing an animal model of NGLY1 deficiency. As germline deletion of NGLY1 is embryonically lethal in mice, Yang et al. (2025) produced a whole-body, inducible knockout of the gene by utilizing UBC-Cre-ER^{T2} mice crossed to *Ngly1*$^{fl/fl}$ animals (hereafter referred to as *iNgly1*$^{-/-}$ mice). Compared with Cre-negative littermate controls, *iNgly1*$^{-/-}$ animals failed to gain weight, exhibited gross motor deficits, and showed a severely shortened lifespan. The authors next investigated gross changes in central nervous system (CNS) tissue. While no apparent alterations were observed in the spinal cord, the authors found a striking loss of Purkinje cells in the cerebellum, providing a putative basis for the progressive motor symptoms in their model. Based on previous cell culture studies demonstrating that NGLY1 deficiency leads to downstream activation of cGAS-STING signaling (Yang et al., 2018), the authors next crossed *iNgly1*$^{-/-}$ mice to STING global knockout animals to study the role of STING signaling in vivo. Loss of STING led to a profound rescue of Purkinje cell loss at 1 year of age as well as a partial rescue of total lifespan (see figure). Single-nucleus RNA-sequencing (snRNA-seq) comparisons of *iNgly1*$^{-/-}$ animals with and without STING showed a rescue of cholesterol synthesis pathways in Bergmann glia, a subtype of astrocytes found in the cerebellum, which may indicate a role for these cells in mediating disease.

Taking advantage of their novel mouse model, the authors next investigated the therapeutic efficacy of treatment with the recently developed STING antagonist VS-X4. Here, the authors observed that oral treatment with VS-X4 starting at 1 mo of age leads to a rescue in both lifespan and Purkinje cell numbers. This provides evidence that targeting STING signaling may be a viable therapeutic approach to slow disease progression, which is the first potential therapeutic of its kind for the treatment of NGLY1 deficiency.



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In addition to the pioneering work defining the in vivo pathophysiology of this devastating neurological disease, this study by Yang et al. (2025) also introduces several exciting new perspectives on the role of STING signaling in neurological disease. While the cGAS-STING pathway was originally identified as a conserved innate immune pathway necessary for pathogen defense, it has now been widely implicated in human diseases across organ systems including in multiple neurological disorders and neurodegenerative diseases. Numerous reviews on cGAS-STING signaling have been published (Jeltema et al., 2023); however, in short, canonical STING activation is downstream of cGAS binding of cytosolic DNA. STING activation leads to the mobilization of TANK-binding kinase 1 (TBK1), which further activates NF-κB and IRF3 transcriptional activity, leading to the release of proinflammatory cytokines

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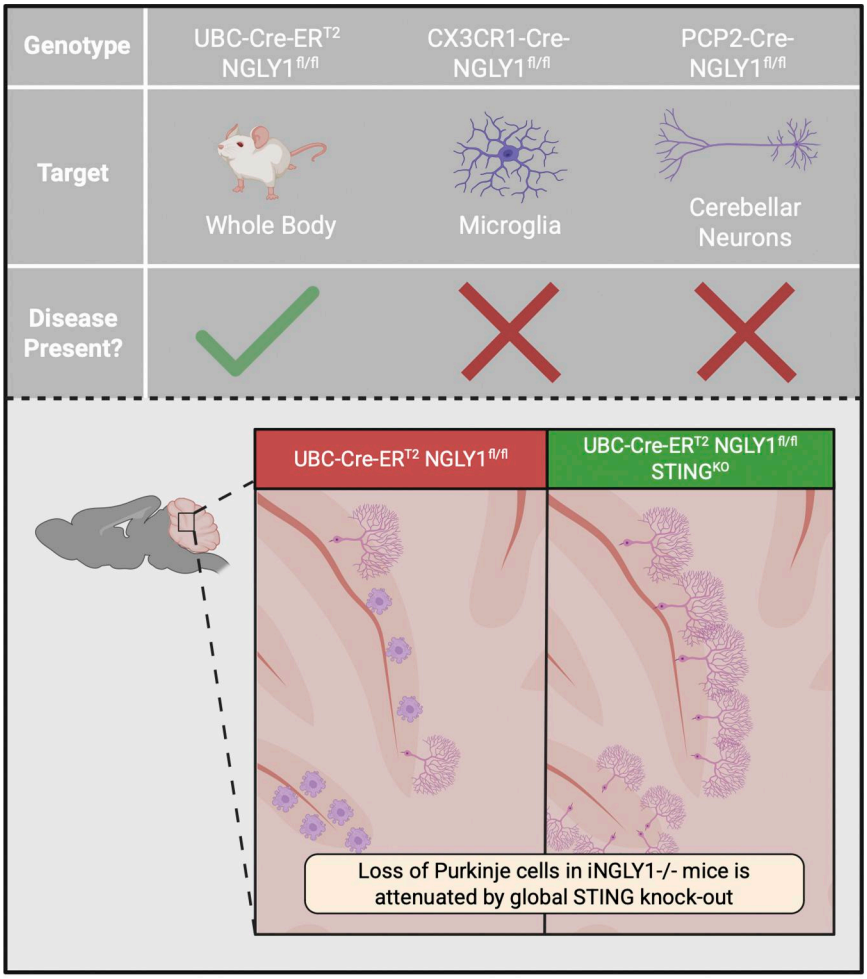

Top panel: Loss of NGLY1 globally, but not in microglia or cerebellar neurons, causes disease resembling human NGLY1 deficiency in mice. It remains an open question whether there is a primary cell type in which loss of NGLY1 can drive disease or if multiple cell types contribute to neurodegeneration. Bottom panel: Germline STING knockout rescues loss of Purkinje cells in the cerebellum of *iNGLY1*$^{-/-}$ mice. The authors demonstrate that treatment with the STING antagonist VS-X4 also attenuates disease, thus providing evidence for a potential novel therapy for disease.

and expression of interferon-stimulated genes.

In models of Parkinson's (Hinkle et al., 2022) and Alzheimer's disease (Xie et al., 2023; Thanos et al., 2025), loss or inhibition of STING ameliorates pathological inflammatory changes that result in microglial activation, loss of synapses, degeneration, and neurological dysfunction. These changes appear driven at least in part by microglia, the brain's resident macrophage population. Unexpectedly, *iNgly1*$^{-/-}$ mice did not show signs of overt neuroinflammation. Bulk RNA-sequencing of cerebellar tissue showed no appreciable changes to interferon-stimulated genes typically expressed downstream of STING, and despite the widespread loss of Purkinje cells, there was no evidence of alterations in microglia activation either by morphology or expression of activation markers such as CD68. This may point to a heretofore unrecognized mechanism of STING-mediated neurodegeneration. Non-inflammatory consequences of STING signaling include activation of autophagy (Gui et al., 2019) and alterations in cellular redox balance (Woo et al., 2024). Interestingly, alterations in both autophagy (Palmer et al., 2025) and cellular redox balance are known to impact neuronal survival (Woo et al., 2024), and this may provide a mechanistic basis to explain how STING can promote neurodegenerative disease progression independent of its canonical effects on proinflammatory cytokine production.

This work also lays the groundwork for clinical application of STING antagonists to target STING-mediated disease and specifically to slow progression of NGLY1 deficiency. The authors used an orally bioavailable compound, VS-X4 (Huffman et al., 2020), to inhibit STING signaling. This approach provides significant advantages over the commonly used STING antagonist H-151, which has a low reported bioavailability and off-target effects (Pan et al., 2021). The authors first validated VS-X4 in TREX1-deficient animals, which develop a GAS-STING–dependent autoimmune disease that models Aicardi-Goutières syndrome and Chilblain lupus in humans (Zhou et al., 2022). VS-X4 treatment suppressed serum autoantibodies, rescued aberrant inflammatory cytokine production, and extended survival of TREX1-deficient animals. VS-X4 treatment also showed promising efficacy in *iNgly1*$^{-/-}$ animals, which taken together suggests that targeting STING using orally bioavailable compounds may offer a viable strategy to treat a range of STING-driven diseases.

Finally, Yang et al. also describe an unexpected result that opens the door to further study of NGLY1 deficiency. To characterize which cell types mediate neurological disease progression in *iNgly1*$^{-/-}$ mice, the authors generated cell-specific knockouts in either microglia or cerebellar neurons utilizing CX3CR1-Cre and Pcp2-Cre mouse lines, respectively. However, neither deletion of NGLY1 in microglia nor neuronal populations led to discernable disease (see figure). This suggests that another cell type, which may or may not be restricted to the CNS, can drive neurodegeneration in disorders of NGLY1 deficiency. Given that NGLY1 and STING are both highly expressed in endothelial cells, it is feasible that endothelial cells could be important players in NGLY deficiency pathogenesis (Zhang et al., 2014).

It is also possible that NGLY1 deficiency and pathological STING activation may be operating in disparate cell types to drive neurodegenerative disease. The study by Yang and colleagues points towards a potential role for Bergmann glia in NGLY1 deficiency. More specifically, when comparing

cerebella from WT, *iNgly1*$^{-/-}$, and *iNgly1*$^{-/-}$ STING$^{-/-}$ mice using snRNA-seq, loss of STING appears to rescue alterations found in cholesterol pathways of Bergmann glia in *iNgly1*$^{-/-}$ animals but did not rescue the alterations in proteasome and autophagy pathways exhibited by glia and neurons in NGLY1-deficient mice. Ultimately, further studies on the role of both NGLY1 and STING in other cell types will be required to disentangle how crosstalk between cells contributes to neurodegeneration in the absence of overt neuroinflammatory changes. Additionally, discerning how STING is activated will yield important insights into the biology of NGLY1 deficiency. While cGAS canonically activates STING, emerging evidence also indicates that STING can be activated in a cGAS-independent fashion in response to aberrant vesicular trafficking, endoplasmic reticulum stress, and endolysosomal dysfunction (Jeltema et al., 2023). Determining whether STING-mediated neurodegeneration is dependent on cGAS will help to unravel the proximate cause of STING activation and yield insights into the origins of non-inflammatory STING activity in NGLY1 deficiency disorder.

In summary, this work improves our understanding of a devastating and rare neurological disease and provides promising evidence for a therapeutic target for those with NGLY1 deficiency. Furthermore, these new findings highlight the need to re-evaluate the full spectrum of ways in which STING can incite neurodegenerative disease pathogenesis. More specifically, while previous work suggests that STING contributes to neurological disease by orchestrating microglial activation and neurotoxic inflammatory changes, the recent study by Yang and colleagues now also indicates that STING-mediated signaling can provoke the loss of neurons and neurological deficits through non-inflammatory pathways.

Acknowledgments

This work was supported by National Institutes of Health grants R01AG071996, R01AG087406, and RF1AG078684 (J.R. Lukens) and T32GM007267 (A. Mangalmurti).

Author contributions: A. Mangalmurti: conceptualization, visualization, and writing—original draft, review, and editing. J.R. Lukens: conceptualization, funding acquisition, and writing—original draft, review, and editing.

Disclosures: The authors declare no competing interests exist.

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