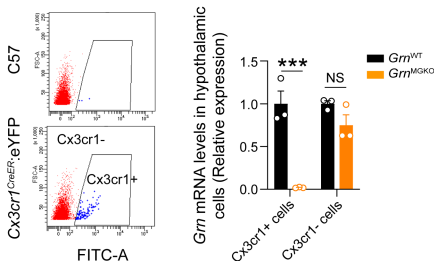
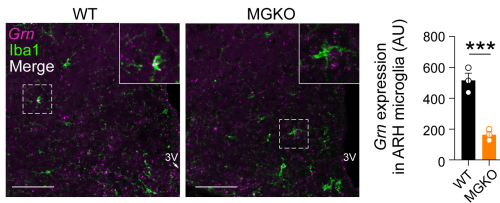


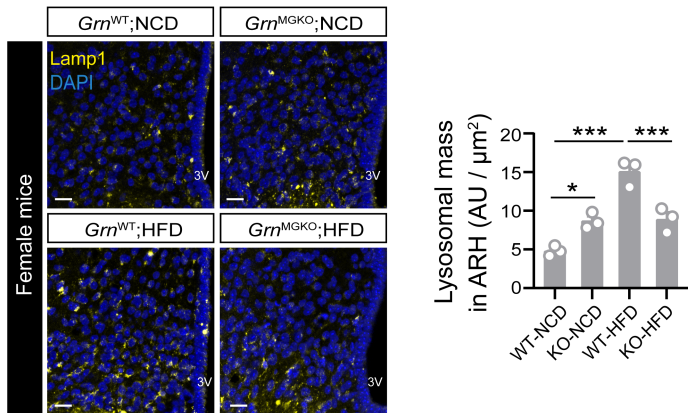
A**B**

Supplementary Figure 1. Confirmation of successful *Gm* knockdown in hypothalamic microglia

A. FACS sorting and then *Gm* qPCR analysis of Cx3cr1:eYFP⁺ and Cx3cr1:eYFP⁻ cells from the hypothalamus of *Gm*^{MGKO} and Cx3cr1^{CreER}:eYFP mice (n = 3).

B. *Gm* FISH followed by Iba1 immunostaining in the hypothalamic arcuate nucleus (ARH) of *Gm*^{MGKO} and *Gm*^{WT} mice (n = 3). Scale bars, 50 μ m.

Results are presented as a mean value $\pm$ SEM. *** p < 0.001. NS, not significant. 3V; 3rd ventricle



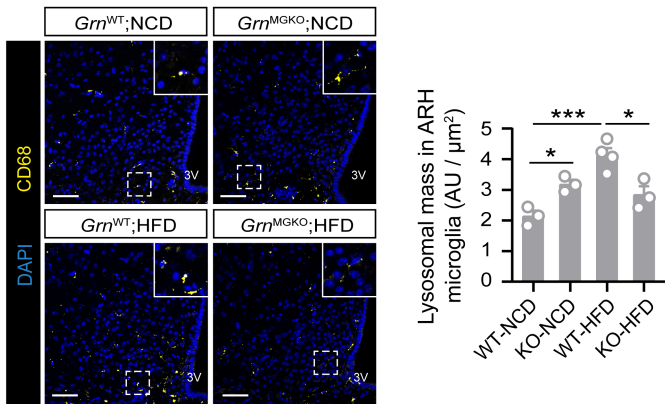
Supplementary Figure 2. Changes in hypothalamic lysosomal mass in female mice with microglial *Grn* deficiency

Representative images and quantification of Lamp1⁺ lysosome mass in the ARH of *Grn*^{WT} and *Grn*^{MGKO} female mice fed an NCD or HFD for 10 weeks (n = 3 mice per group).

Approximately 100 cells per mouse were analyzed. Scale bars, 20 μm .

Results are presented as a mean value $\pm$ SEM. * $p < 0.05$, and *** $p < 0.001$ between indicated groups.

ARH; the arcuate nucleus of the hypothalamus, NCD; normal chow diet, HFD; high-fat diet.

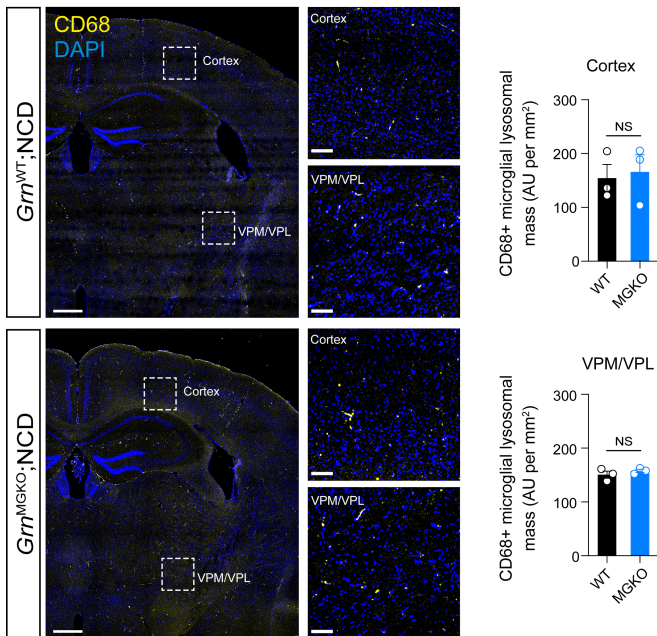


Supplementary Figure 3. Alternations in microglia lysosomal mass in ARH of mice with microglial *Grn* deficiency

Representative images and quantification of CD68⁺ microglia lysosomal mass in the ARH of *Grn*^{WT} and *Grn*^{MGKO} mice fed an NCD or HFD for 10 weeks (n = 3–4 mice per group).

Approximately 100 cells per mouse were analyzed. Scale bars, 50 μm .

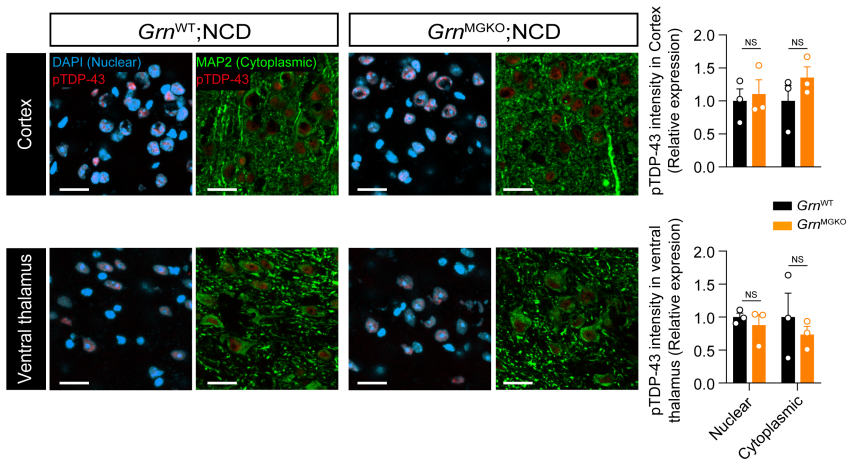
Results are presented as a mean value $\pm$ SEM. **p* < 0.05, and ****p* < 0.001 between indicated groups.



Supplementary Figure 4. Unaltered microglia lysosomal mass in the cortex and ventral thalamus of young mice with microglial *Grn* deficiency

Representative images and quantification of CD68⁺ microglia lysosomal mass in the cortex and ventral thalamus of 17 week-old *Grn*^{WT} and *Grn*^{MGKO} mice fed an NCD (n = 3).

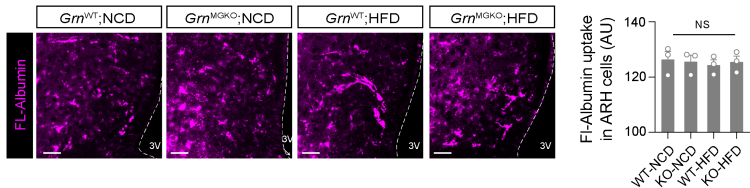
Scale bars, 500 μ m (left panel) and 300 μ m (right panel). Results are presented as a mean value $\pm$ SEM. NS, not significant. VPL; ventral posterolateral nucleus of thalamus, VPM; ventral posteromedial nucleus of thalamus,



Supplementary Figure 5. pTDP-43 expression in the cortex and ventral thalamus of young mice with microglial *Grn* deficiency

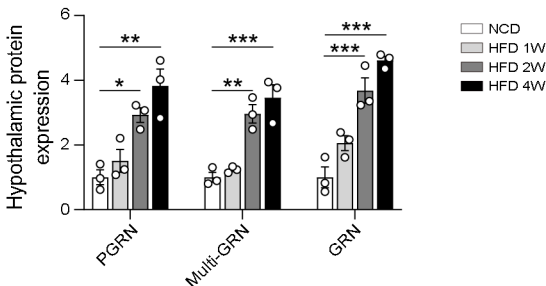
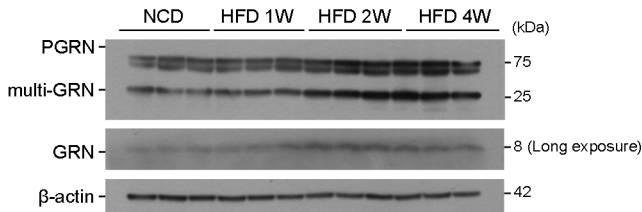
Representative images and quantification of nuclear and cytoplasmic pTDP-43 expression in the cortex and ventral thalamus of 17 week-old *Grn*^{WT} and *Grn*^{MGKO} mice fed an NCD ($n = 3$).

Scale bars, 20 μ m. Results are presented as a mean value $\pm$ SEM. NS, not significant.



Supplementary Figure 6. A deficiency of microglial PGRN does not affect uptake of fluorescence (FI)-labeled albumin

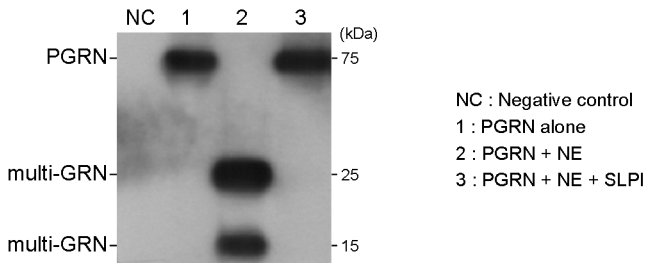
Representative images and measurements of FI-albumin uptake in the ARH cells of *Grn*^{WT} and *Grn*^{MGKO} mice fed with an NCD or HFD for 10 weeks. About 100 ARH cells per mouse were analyzed (n = 3 mice). Scale bars, 20 μ m. Results are presented as a mean value $\pm$ SEM. NS, not significant.



Supplementary Figure 7. Increased hypothalamic PGRN cleavage in the HFD-fed mice

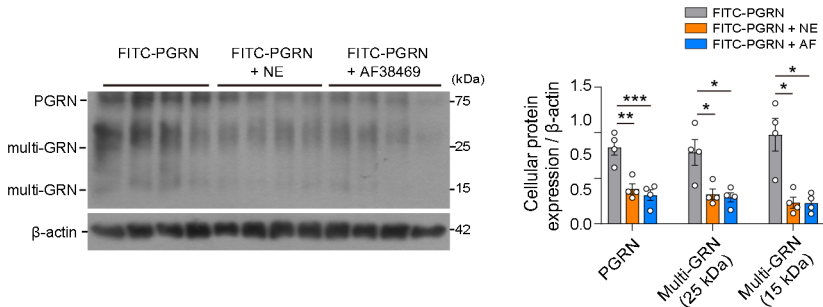
PGRN and GRN immunoblotting of the hypothalamus in C57BL6/J mice fed on an HFD for indicated periods. The data are presented as fold changes relative to the NCD group. Results are presented as a mean value $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ between indicated groups.

kDa; kilodalton.



Supplementary Figure 8. Neutrophil elastase (NE)-induced PGRN cleavage and SLPI-mediated inhibition in vitro

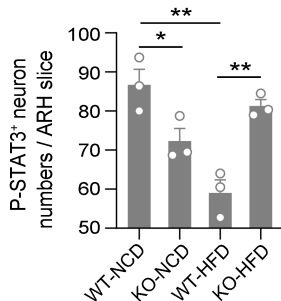
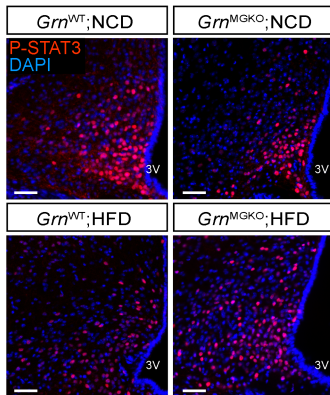
PGRN immunoblotting revealing NE-induced PGRN cleavage and the SLPI-induced reversal of NE-induced PGRN cleavage. SLPI; secretory leukocyte peptidase inhibitor.



Supplementary Figure 9. Intracellular expression of full-length PGRN and cleaved PGRN in N1 hypothalamic cells following treatment with FITC-labeled PGRN

Immunoblotting analysis was performed on lysates of N1 cells treated with FITC-PGRN with or without NE (neutrophil elastase), and sortilin inhibitor AF38469.

Results are presented as a mean value $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ between indicated groups.



Supplementary Figure 10. Leptin-induced STAT3 phosphorylation in the ARH neurons of mice with microglial *Grn* deficiency

Grn^{WT} and *Grn*^{MGKO} male mice were fed an NCD or HFD for 10 weeks and injected with leptin 3 mg/kg intraperitoneally 45 minutes before sacrifice (n = 3 mice). Scale bars, 50 μ m. Results are presented as a mean value $\pm$ SEM. * p < 0.05, ** p < 0.01, and *** p < 0.001 between indicated groups.