NLRP3 inflammasome suppression improves longevity and prevents cardiac aging in male mice

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Published in Aging Cell 09/2019
Impact Factor: 7,3 (2018/19)

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- Introduction/Background Information
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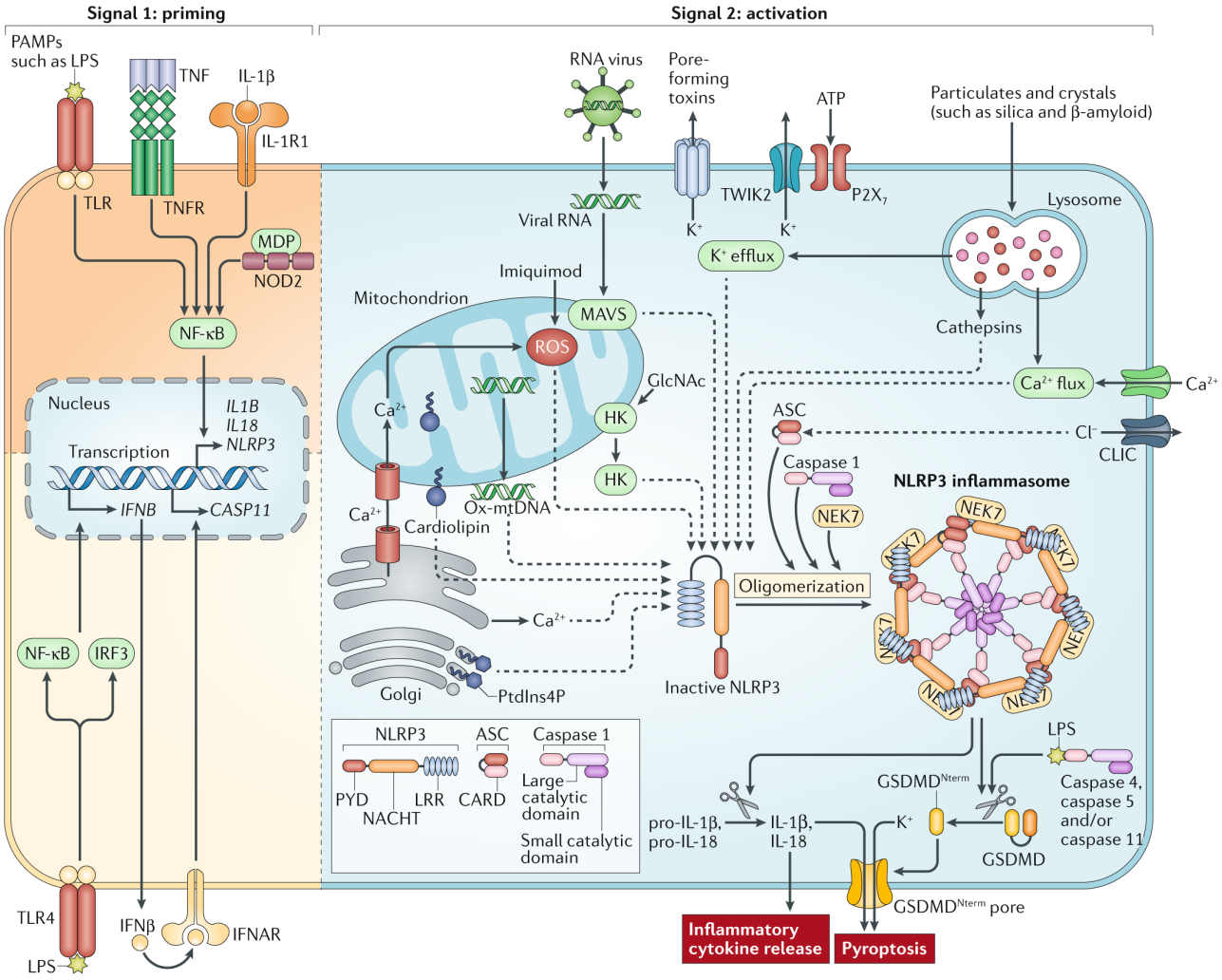
NLRP3 inflammasome/Inflammaging

- Inflammasomes are cytosolic multiprotein oligomers of the innate immune system
  → responsible for the activation of inflammatory responses
- consists of a sensor (NLRP3), an adaptor (ASC; also known as PYCARD) and an effector (caspase 1)
- Activating stimuli include: extracellular ATP release, crystals (urate, cholesterol) and microbial toxins
- Formation of the inflammasome activates caspase 1, which in turn cleaves pro-IL-1β and pro-IL-18 as well as Gasdermin D

NLRP3 inflammasome



The NLRP3 inflammasome: molecular activation and regulation to therapeutics

Materials and Methods

- Mouse experiments

  - Young and old NLRP3−/− transgenic mice (C57BL/6J background) and WT/ NLRP3+/+ controls

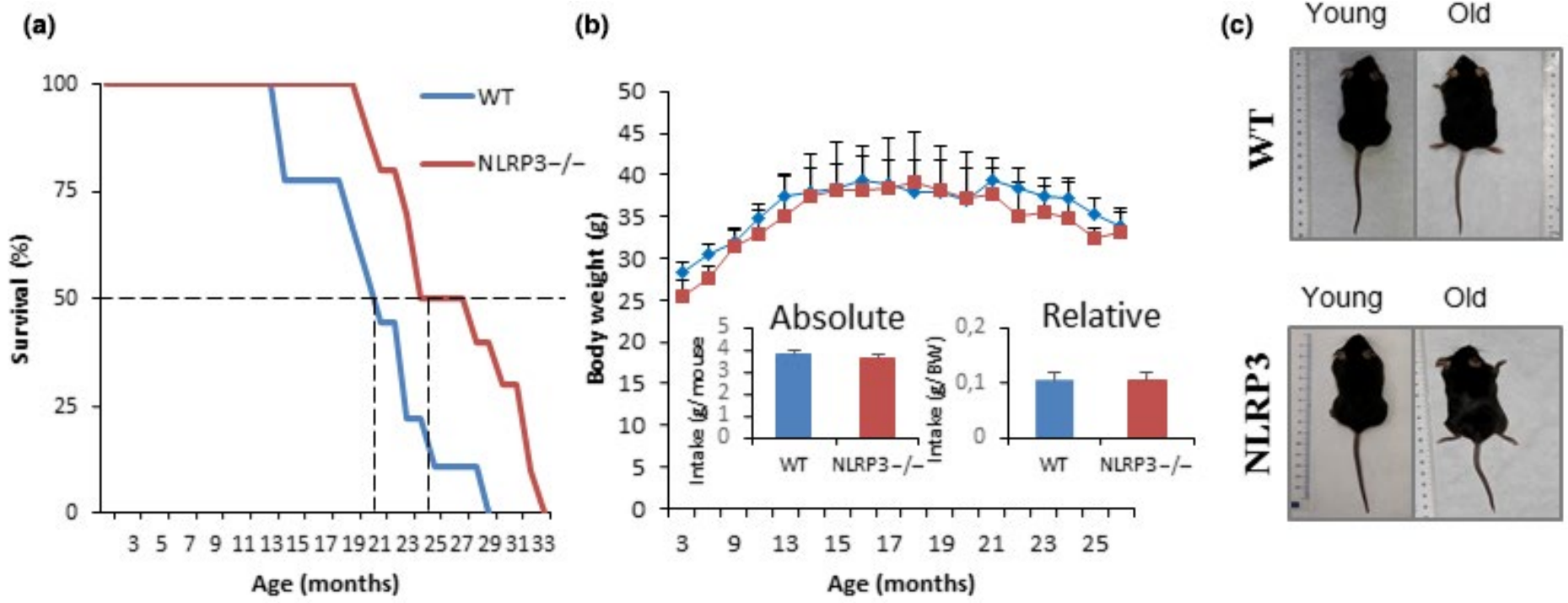
  - housed in groups of four to eight
  - monitored daily and weighed monthly, but were otherwise left undisturbed until they died

- Glucose tolerance test
- ELISA for Leptin Adiponectin and IGF-1
- Electrocardiography, Echocardiography
- Telomere length analysis
- Transcriptome analysis

Results

- NLRP3 deletion improves lifespan and metabolic aging
- NLRP3 deletion preserved cardiac integrity
- Age-associated metabolic changes were prevented in NLRP3−/−
  - Changes in the Pi3K/mTOR pathways and autophagy
- Age-associated change of the cardiac gene expression profile was prevented in NLRP3 −/− mice

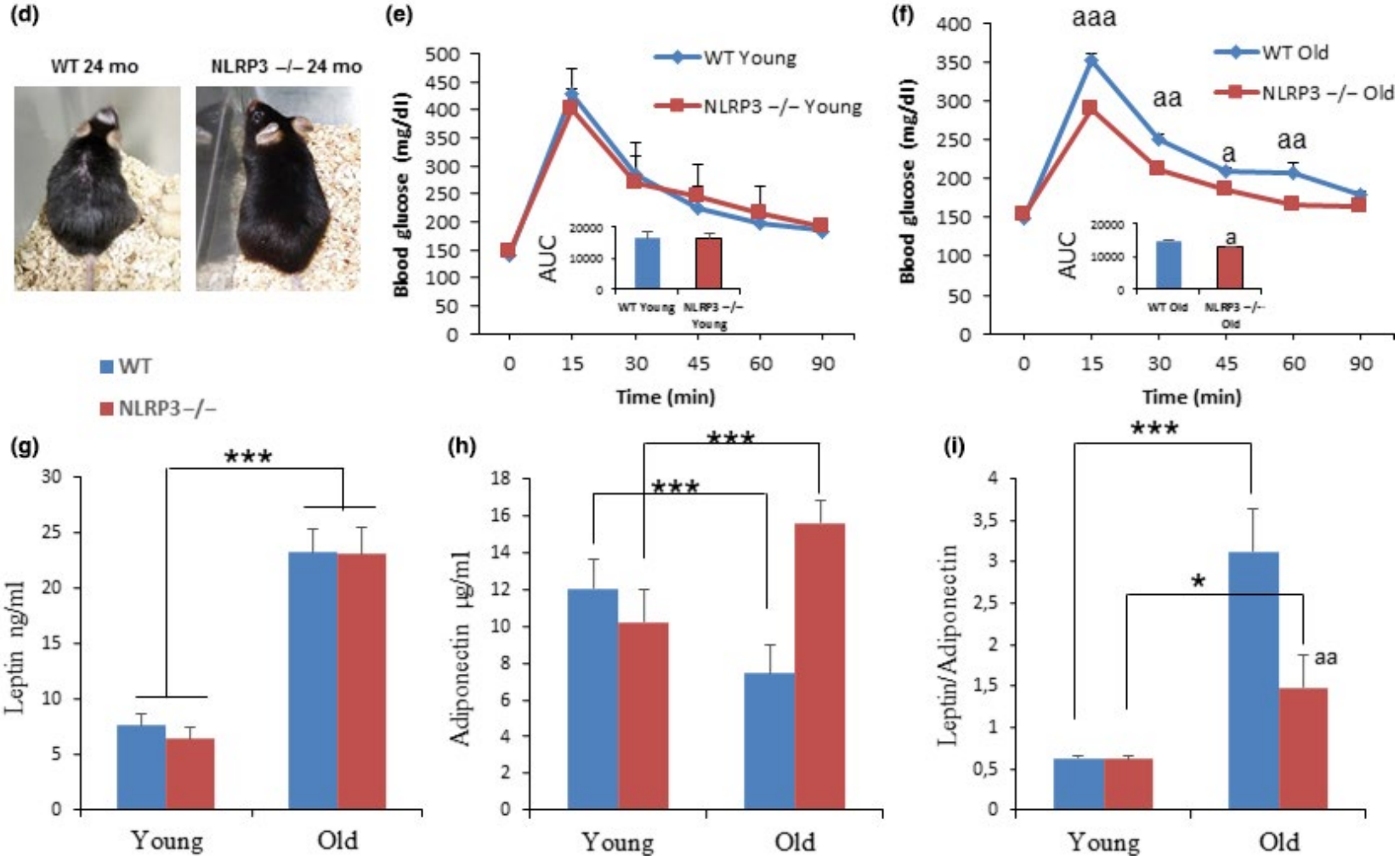
NLRP3 signaling suppression in mice extend lifespan and improve metabolic homeostasis I



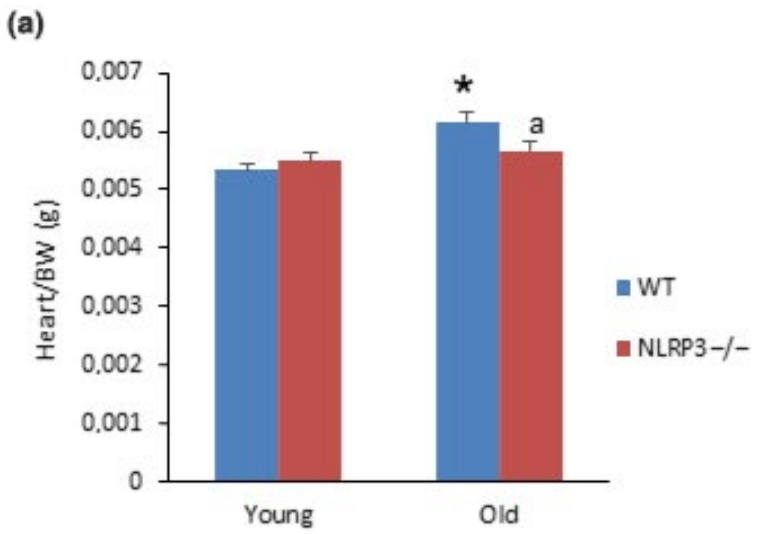
significant increment of the máximum lifespan in WT mice compared with NLRP3 −/− mice

Body weights and average daily oral food intake normalized to body weight and to mouse of the groups over time.

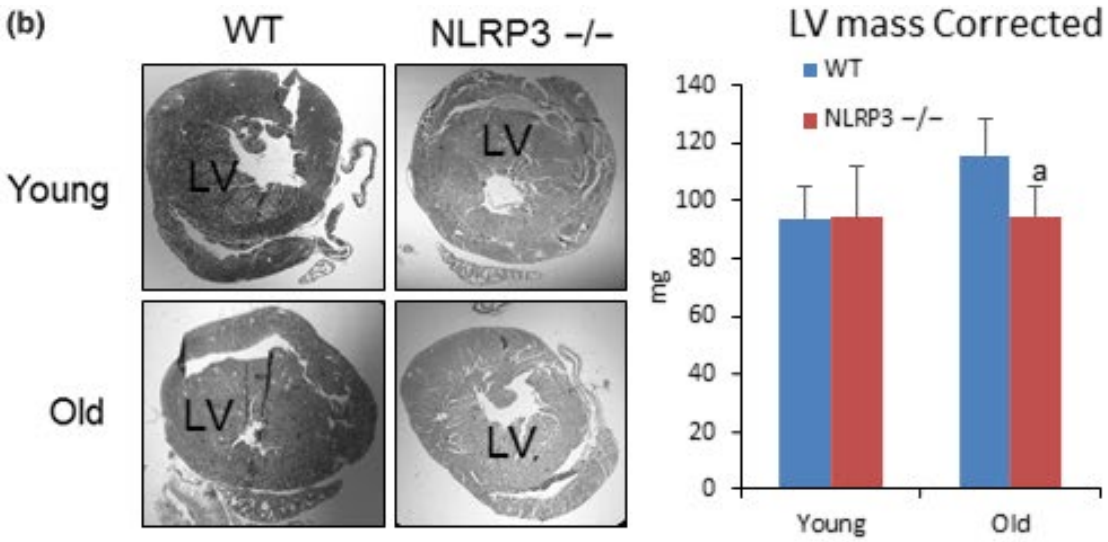
NLRP3 signaling suppression in mice extend lifespan and improve metabolic homeostasis II



NLRP3 signaling suppression in mice induces cardiac protection I

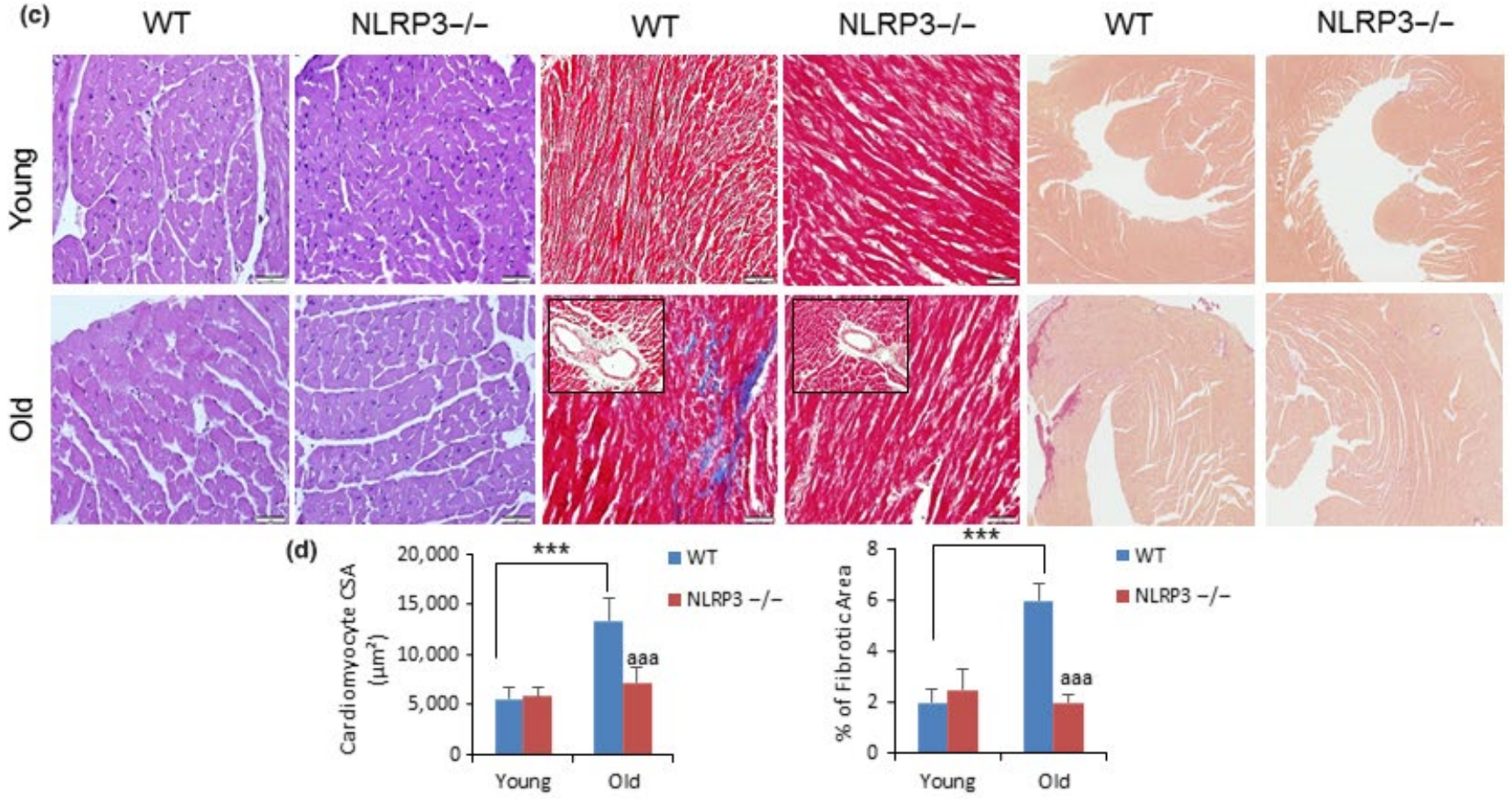


Heart weight normalized to bodyweight.



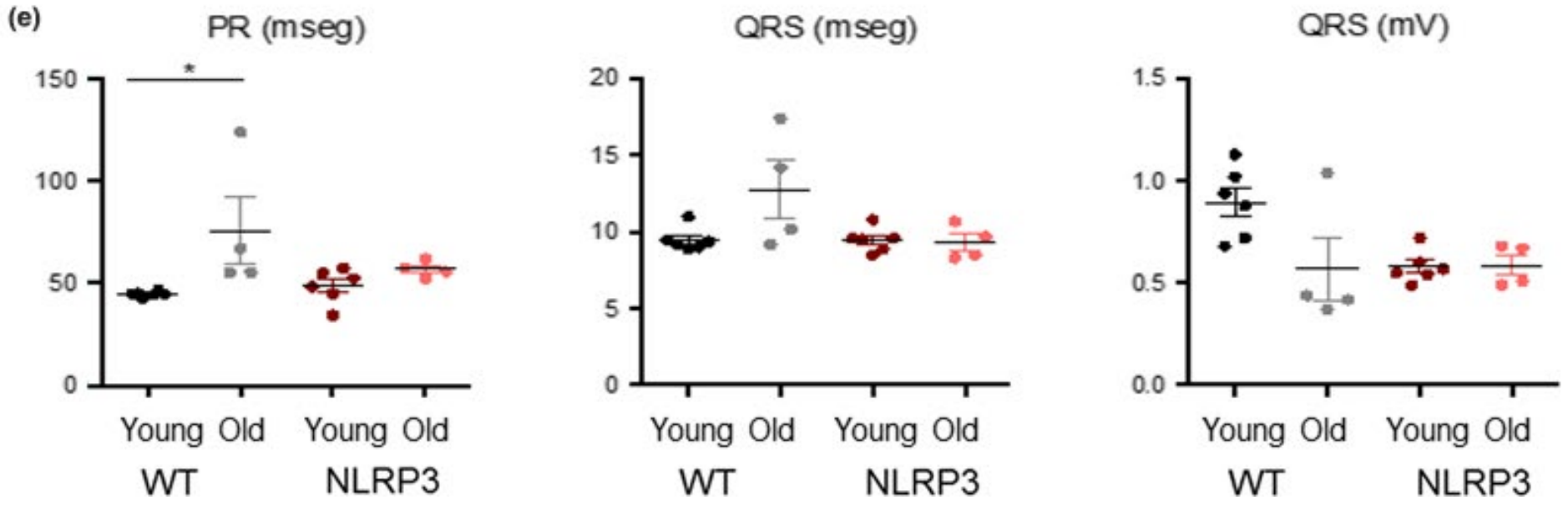
Representative image of centripetal concentric LV hypertrophy

NLRP3 signaling suppression in mice induces cardiac protection II

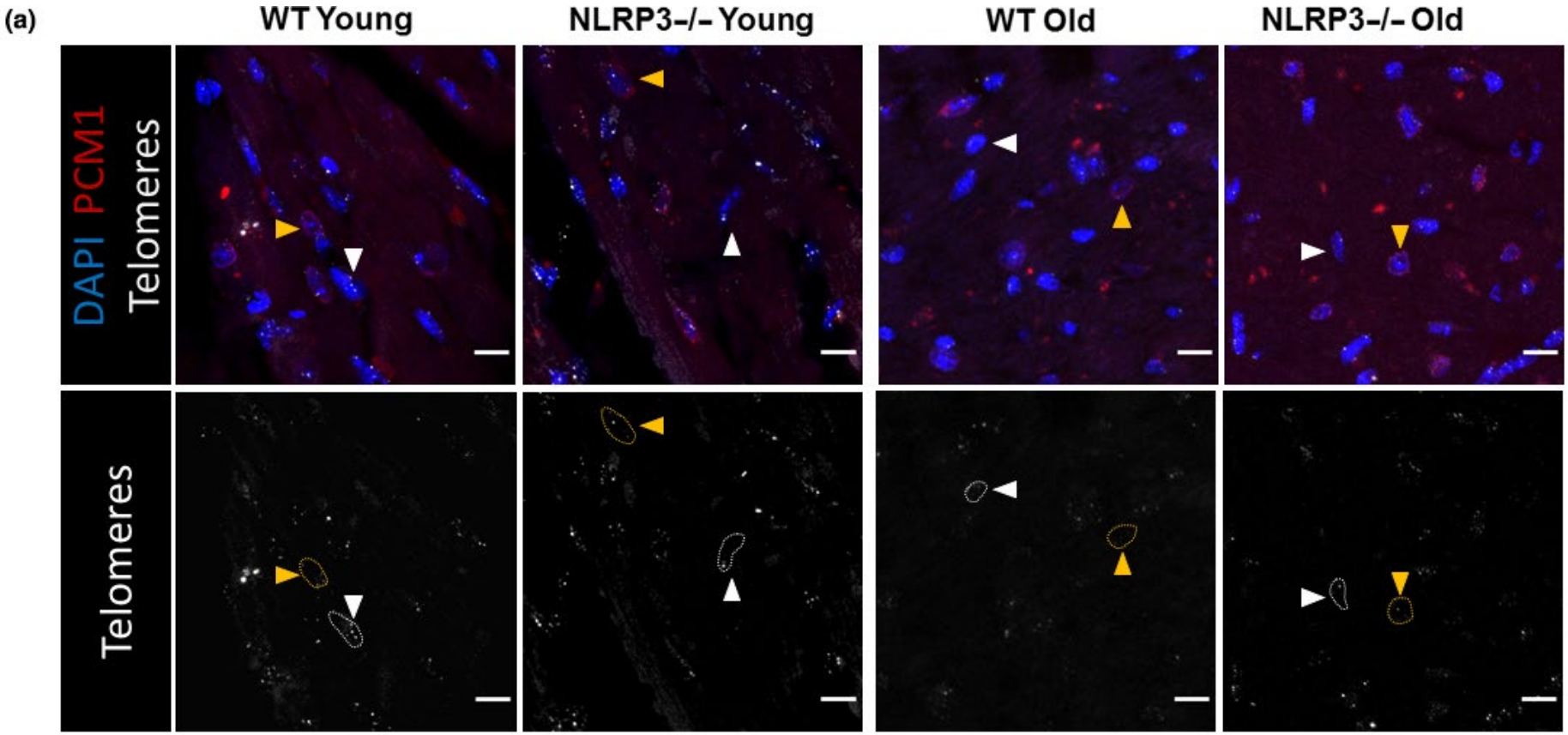


Quantitative analysis of cardiomyocyte cross-sectional (transverse) area with measurements of ≈100 cardiomyocytes and fibrotic areas from 3 to 6 mice per group

NLRP3 signaling suppression in mice induces cardiac protection III

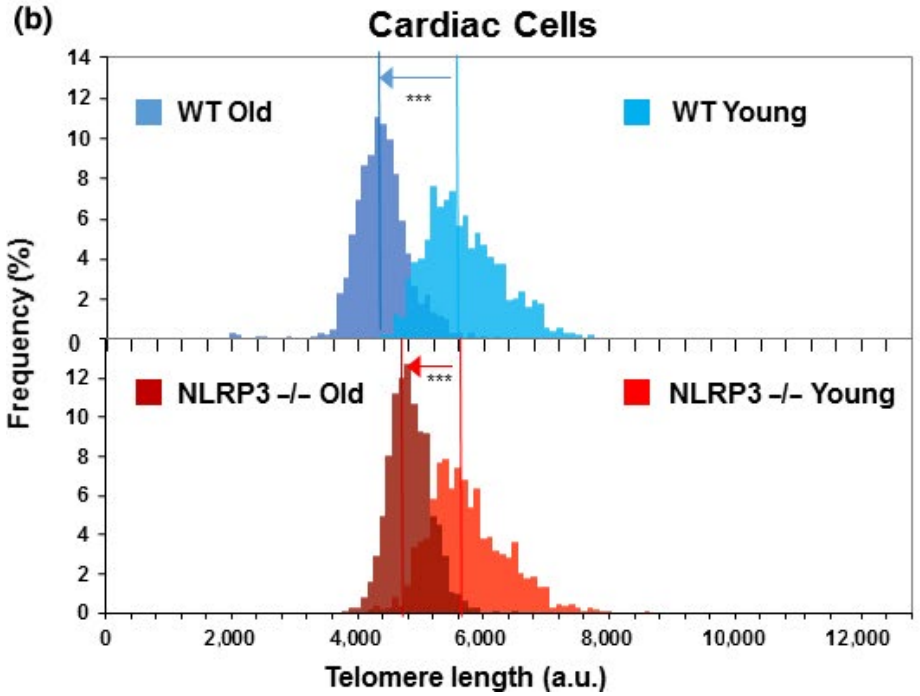


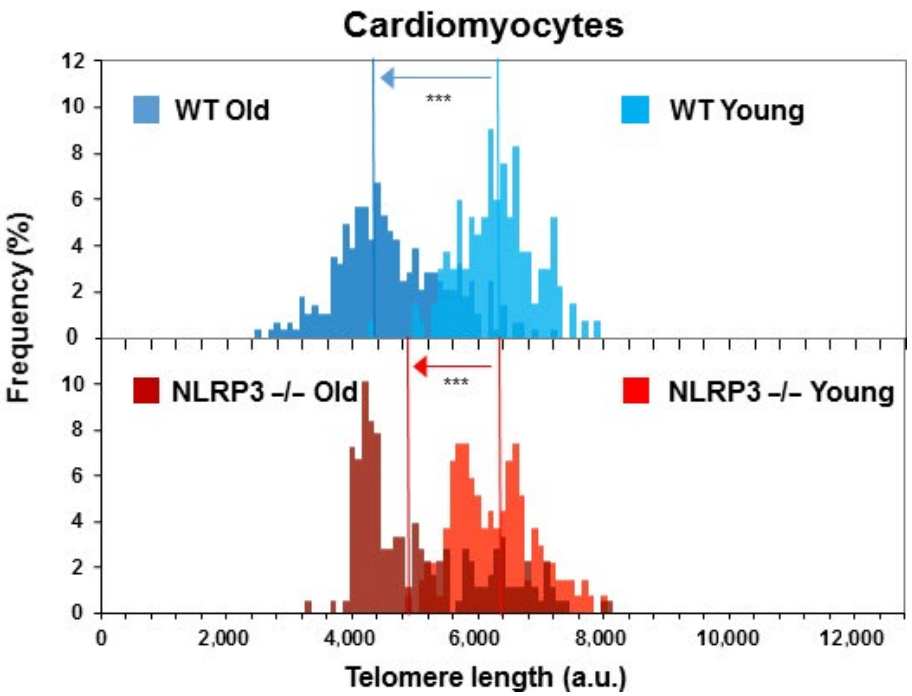
Telomere length differs in cardiac cells from WT and NLRP3−/− mice I



reduced telomere shortening rate in WT mice when compared to NLRP3 −/− mice.

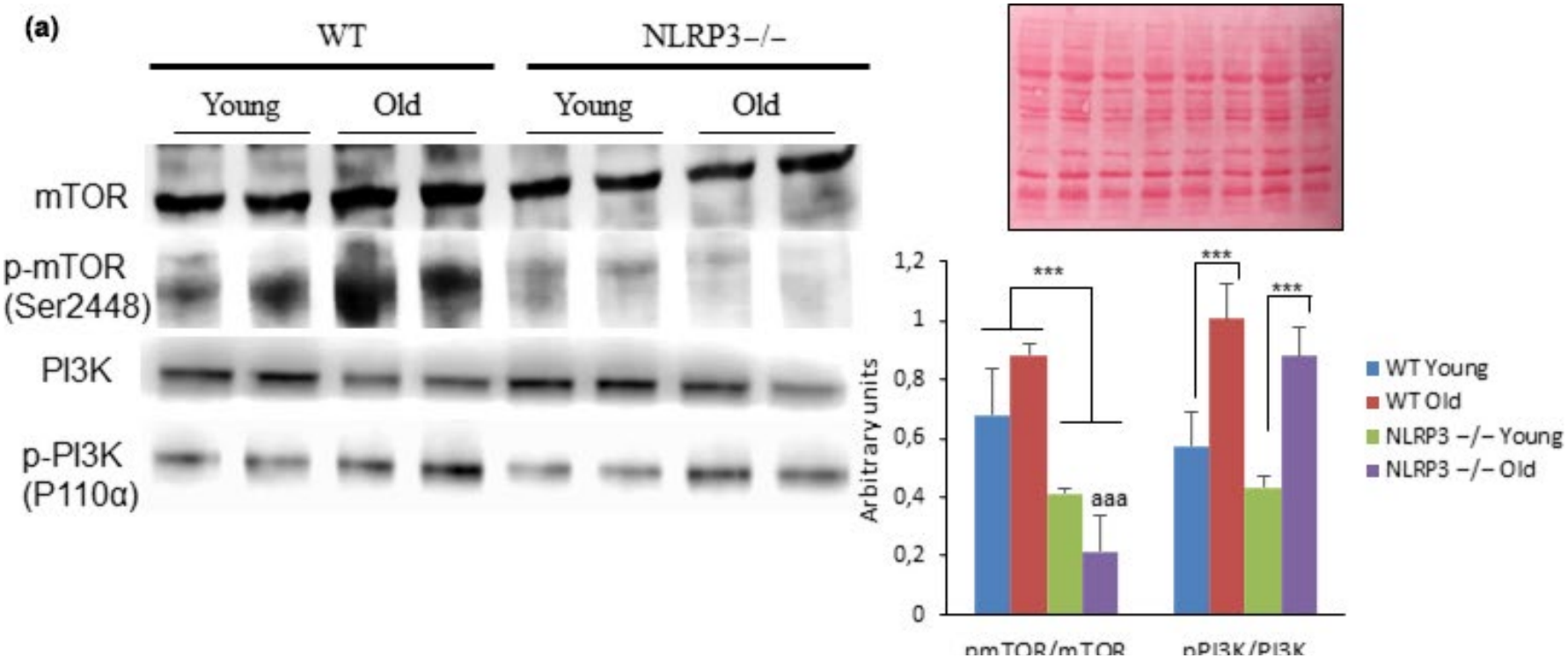
Telomere length differs in cardiac cells from WT and NLRP3−/− mice II





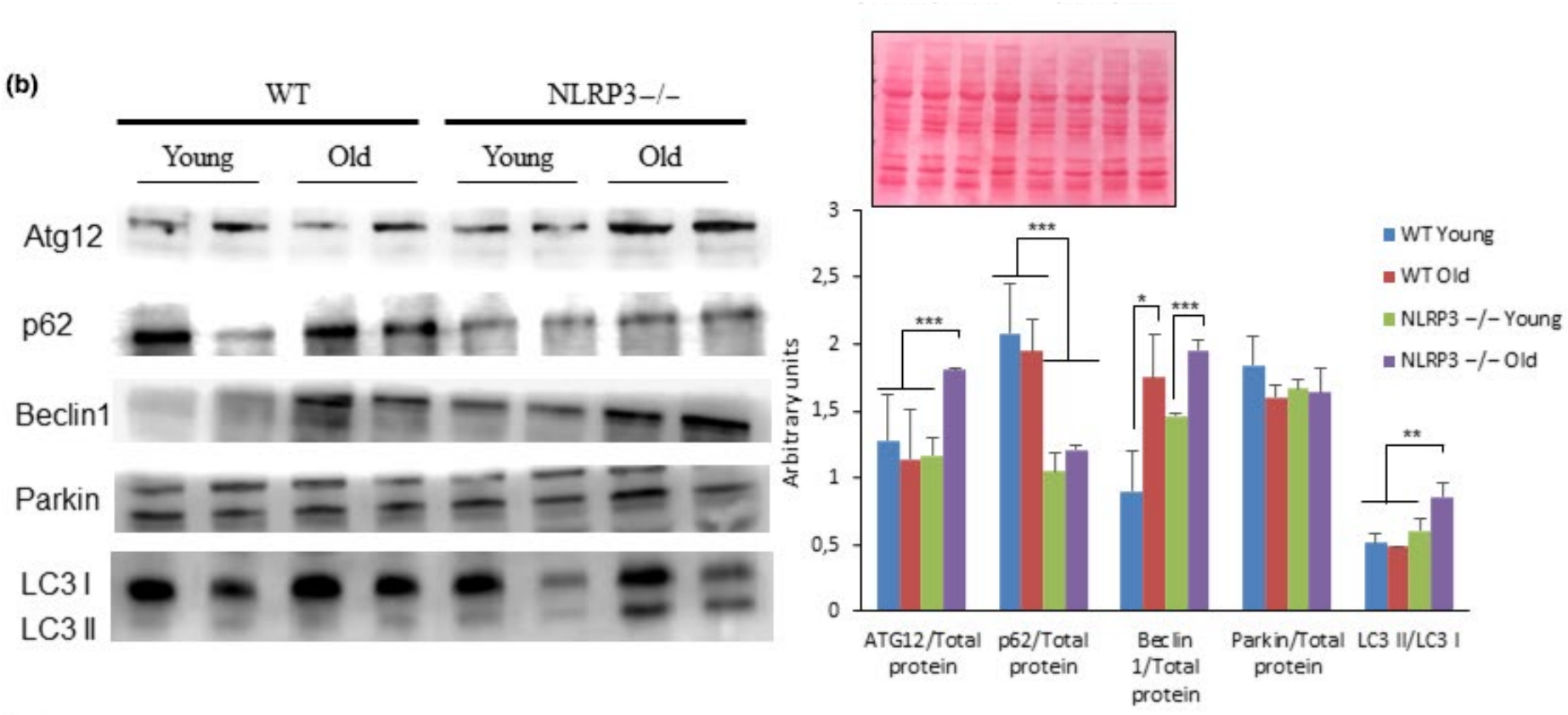
Telomere length distribution in total cardiac cells (left) and cardiomyocytes (right) of young and old WT and NLRP3−/− mice.

Changes in the Pi3K/mTOR pathways and autophagy observed in cardiac tissues from young and old mice I



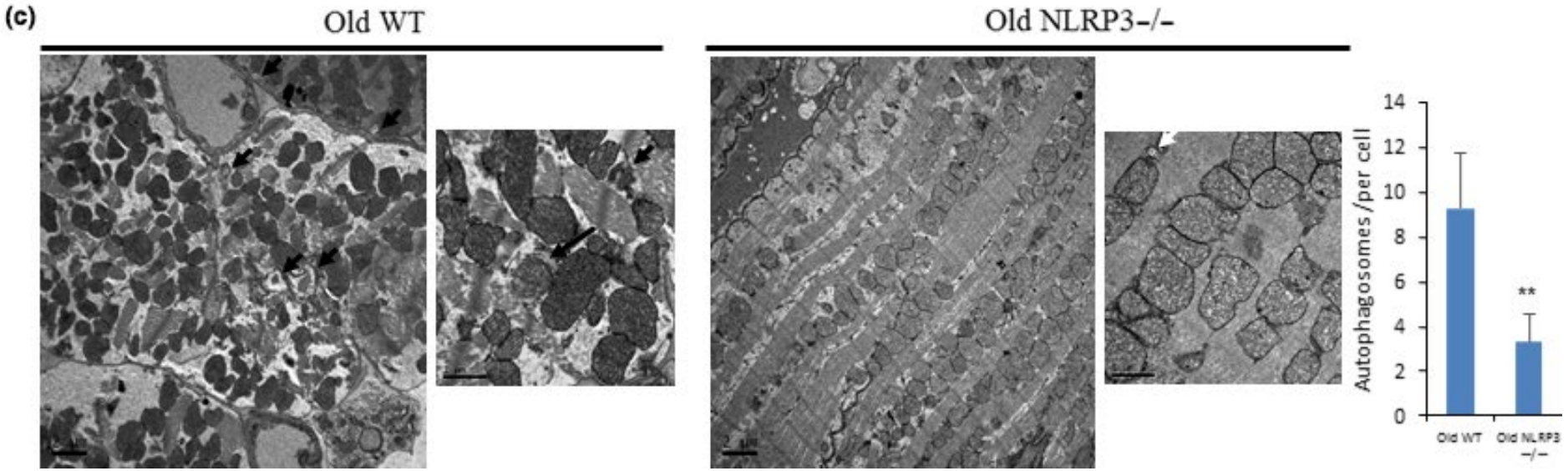
mTOR inhibition is associated with the important physiological process of autophagy

Changes in the Pi3K/mTOR pathways and autophagy observed in cardiac tissues from young and old mice II



Western blot analysis with representative blot including
ATG12, Beclin 1, LC3, Parkin, and p62 level in the heart of Young and old mice

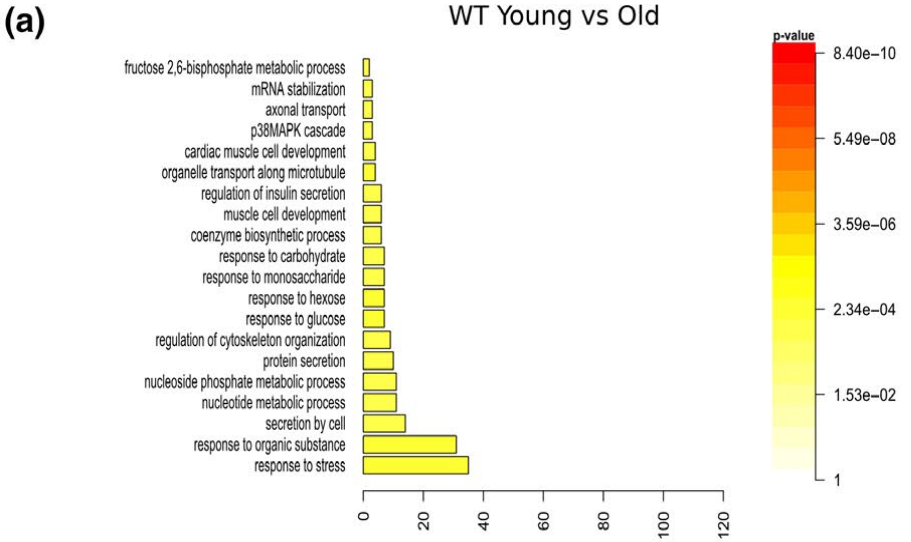
Changes in the Pi3K/mTOR pathways and autophagy observed in cardiac tissues from young and old mice III

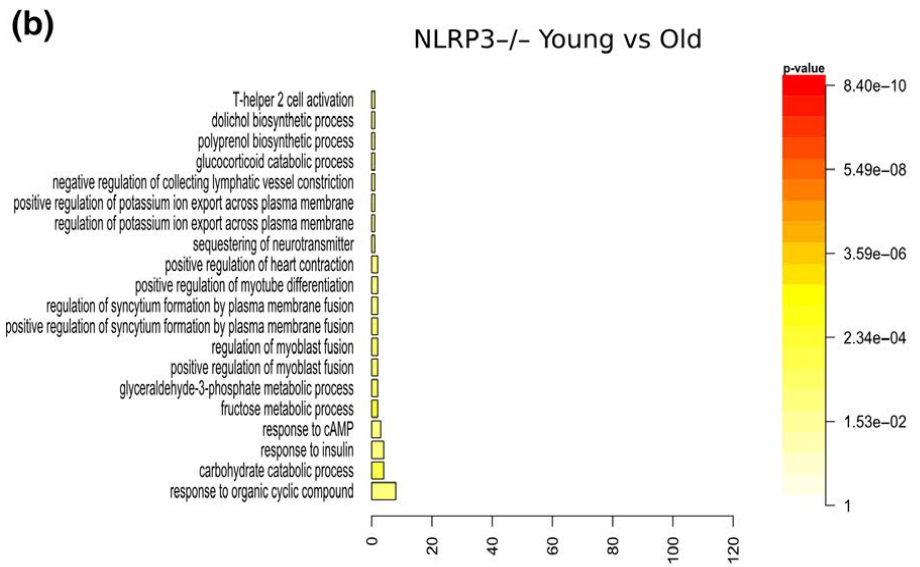


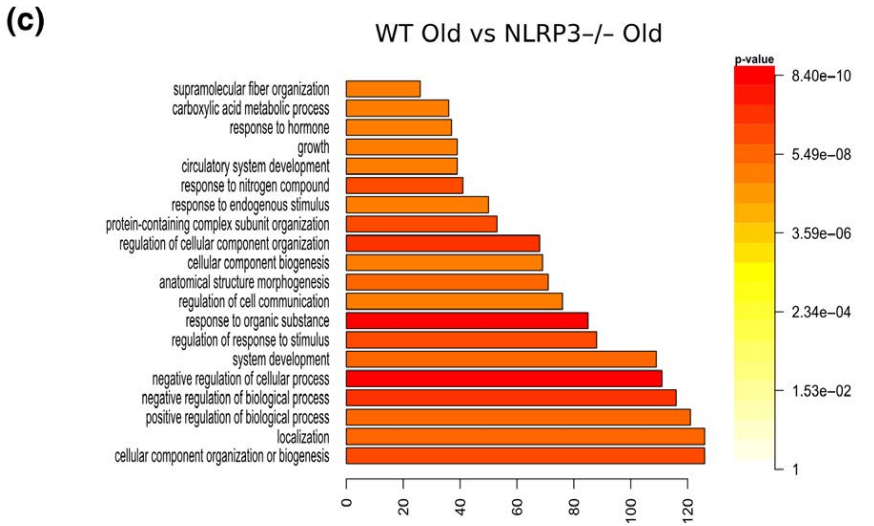
numbers of accumulated autophagosomes were reduced in hearts from NLRP3−/− old mice

improved autophagic flux

Transcriptional changes in heart from Young and old WT and NLRP3−/− mice







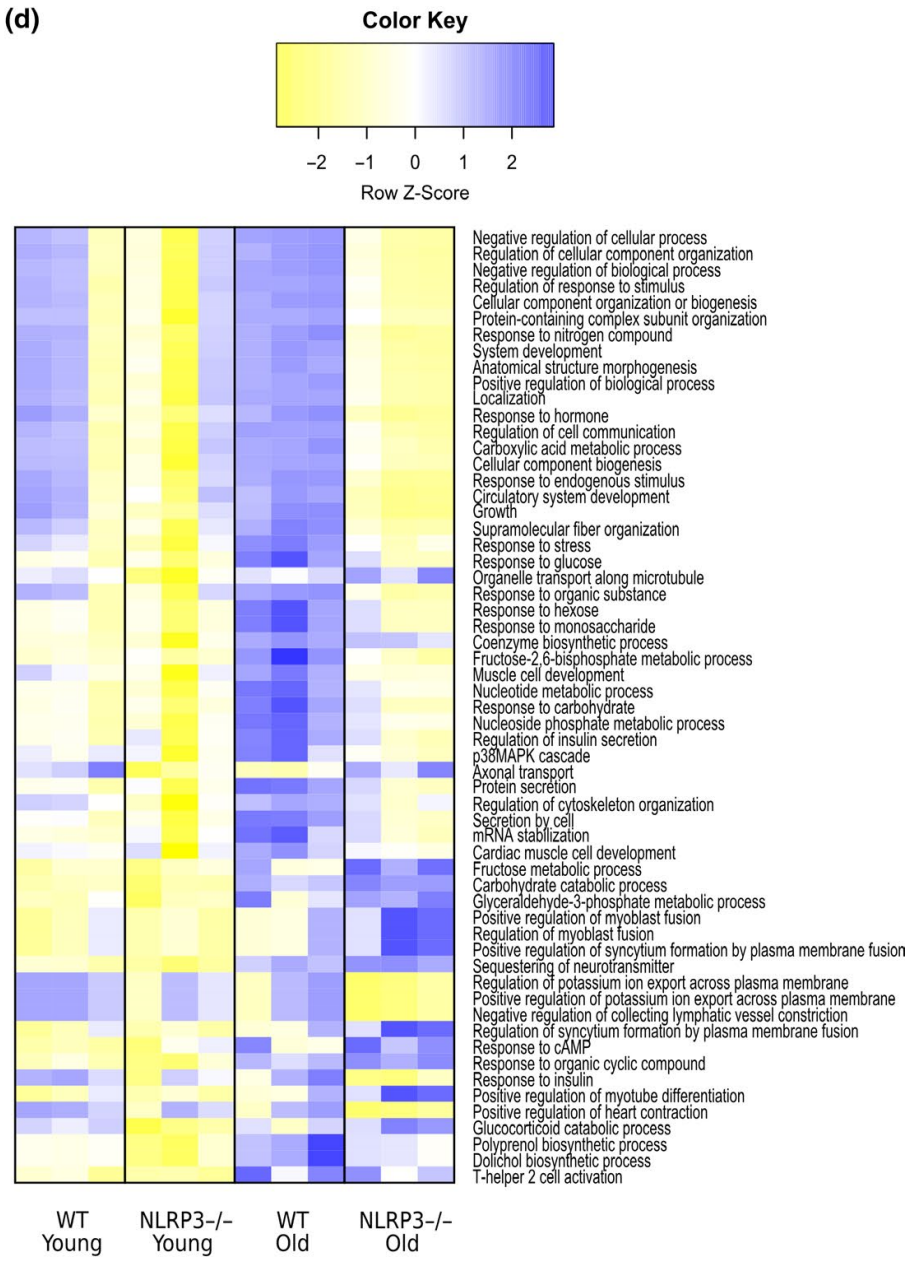
Gene Ontology enrichment analysis

142 transcripts were upregulated and 60 transcripts were downregulated

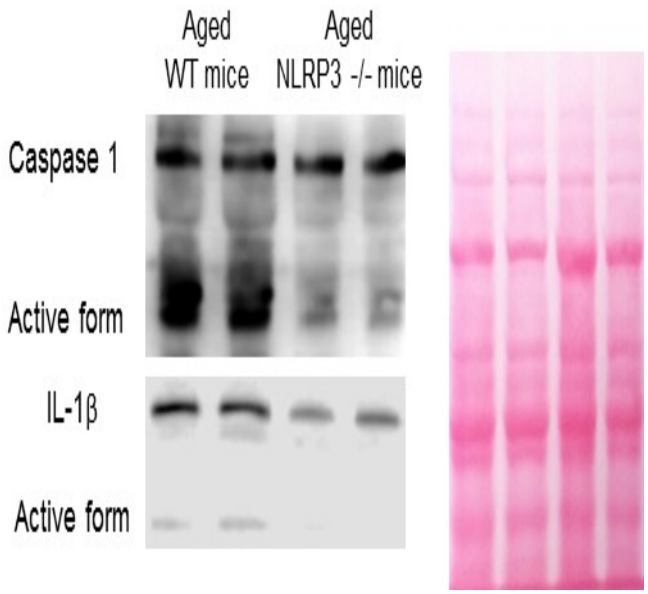
43 pathways were significantly altered be- tween old WT and old NLRP3−/− mice.

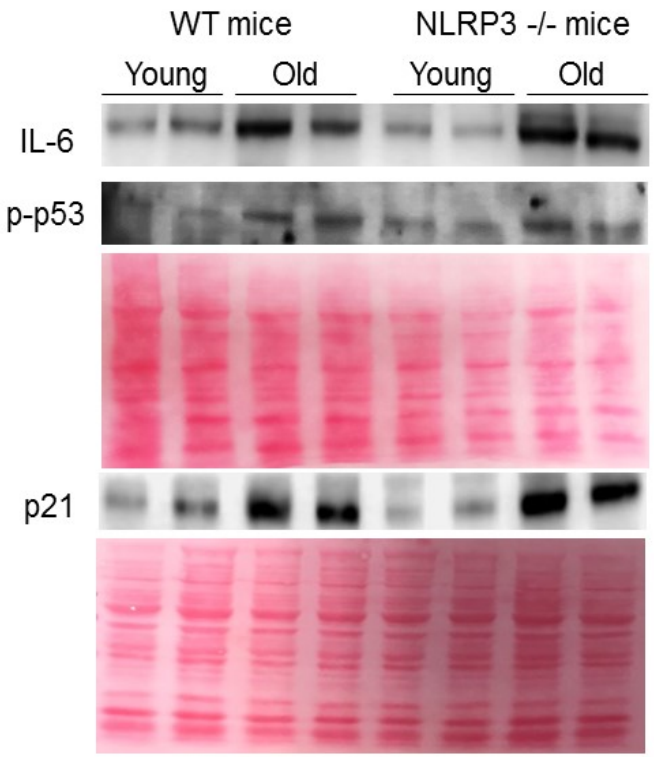
Differentially expressed Genes between WT old vs. NLRP3 −/− old mice (n = 3 per treatment)

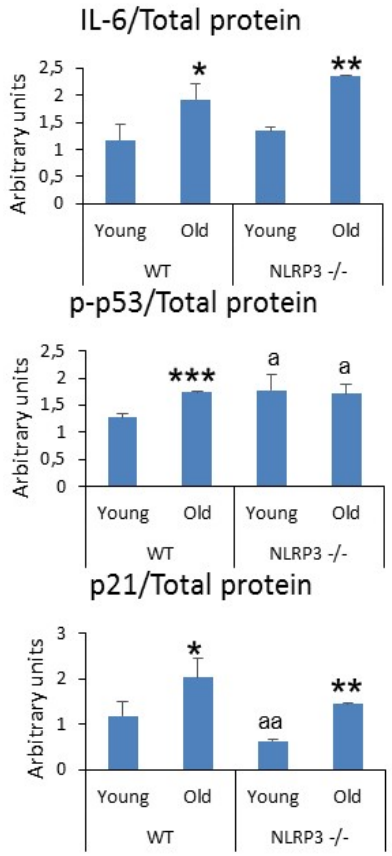
most significant downregulated gene expression in old WT mice compared with old NLRP3 was nicotinamide phosphoribosyl- transferase (Nampt), the rate-limiting enzyme in mammalian NAD+ biosynthesis



Changes in the Caspase activation and release of senescent inflammatory markers







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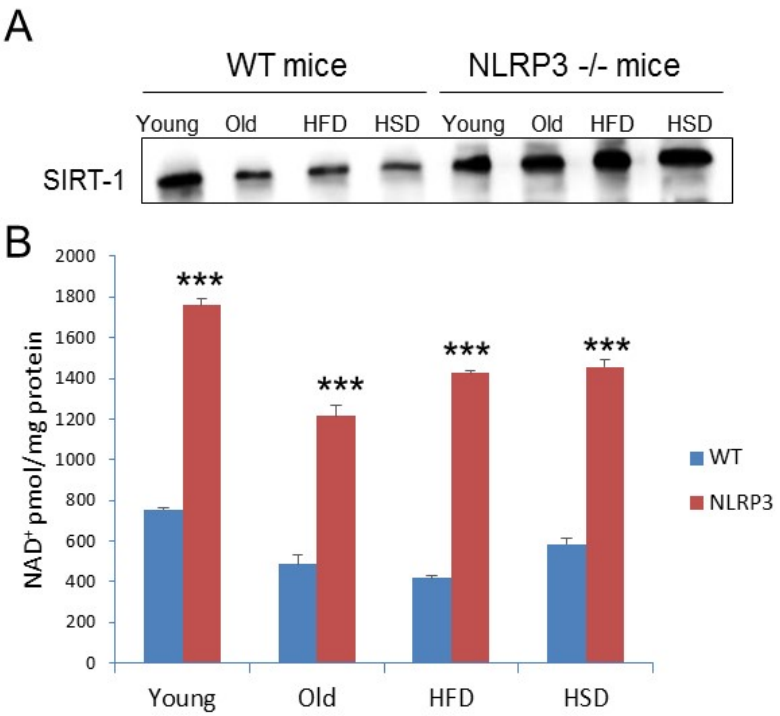

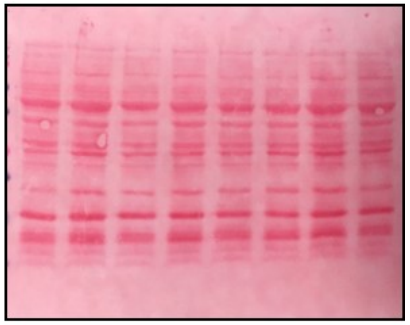

These findings could explain the improved metabolic status and autophagic flux observed in NLRP3−/− mice during aging

Summary

- NLRP3 inhibition atten- uates the harmful effects of cardiac aging and extends the lifespan in male mice.
- NLRP3 ablation improves metabolic characteristics related to aging, such as glucose tolerance, lipid metabolism, and leptin/adiponectin
- ablation of NLRP3 showed low serum levels of IGF-1 in old mice
- NLRP3 ablation also showed inhibition of PI3K/mTOR
- transcriptomic analysis showed reduced IRS-1 expression in old NLRP3 mice and an anti-hypertrophic effect of cardiac protection

Discussion

- Inflammation is highly associated with aging and age-related diseases
- Increased systemic inflammation is commonly concomitant with metabolic alterations
  → increased adiposity, insulin resistance, and dyslipidemia
- Experimental manipulation of a specific inflammatory pathway would entail systemic and metabolic effects with an improvement in life expectancy and health
  → NLRP3 ablation causes an increase in longevity that could be due to several of the metabolic changes induced by this manipulation

Discussion

- These results could be associated with reduced IGF-1 signaling and the PI3K/AKT/mTOR pathway and with auto phagy activation
- NLRP3 inhibition could be associated with a specific inflam-masome-dependent inflammaging

Thank you for your attention