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Supplementary Materials for

Cell identity and nucleo-mitochondrial genetic context modulate OXPHOS performance and determine somatic heteroplasmy dynamics

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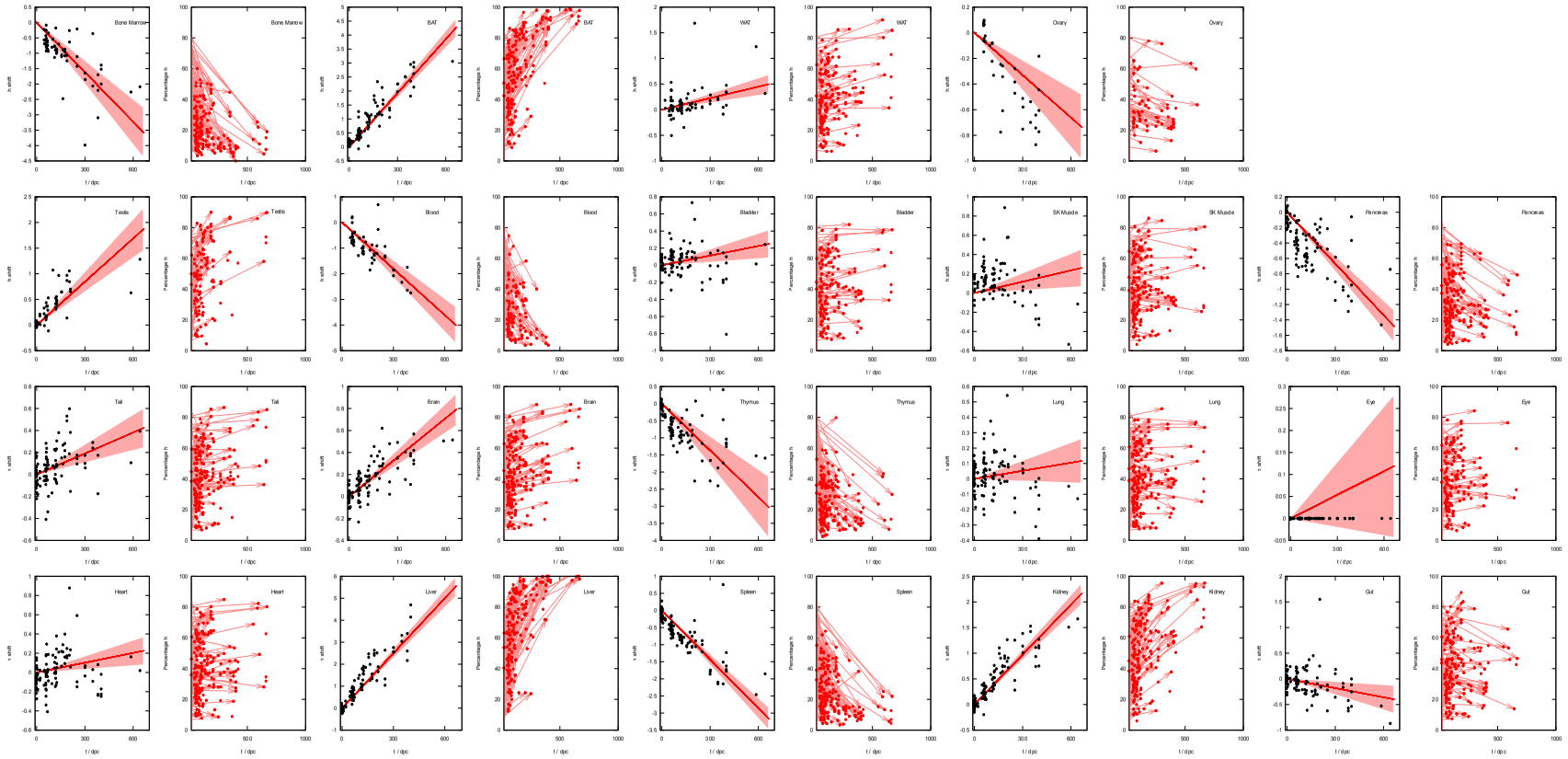

Figure S1. Absolute versus transformed heteroplasmy shift. Transformed heteroplasmy shift plot of the different tissues (left) accompanied by the absolute values plot (right) showing percentage of heteroplasmy for every mouse measurement (each dot corresponds to a different individual). The arrows go from the 21-day tail measurement to the later tissue measurement. In the transformed heteroplasmy shift plots (n=119 BL/6$^{C57\text{-}NZB}$ mice), red lines give inferred mean segregation behavior with 95% confidence intervals and black dots show heteroplasmy data in the given tissue plotted relative to eye.

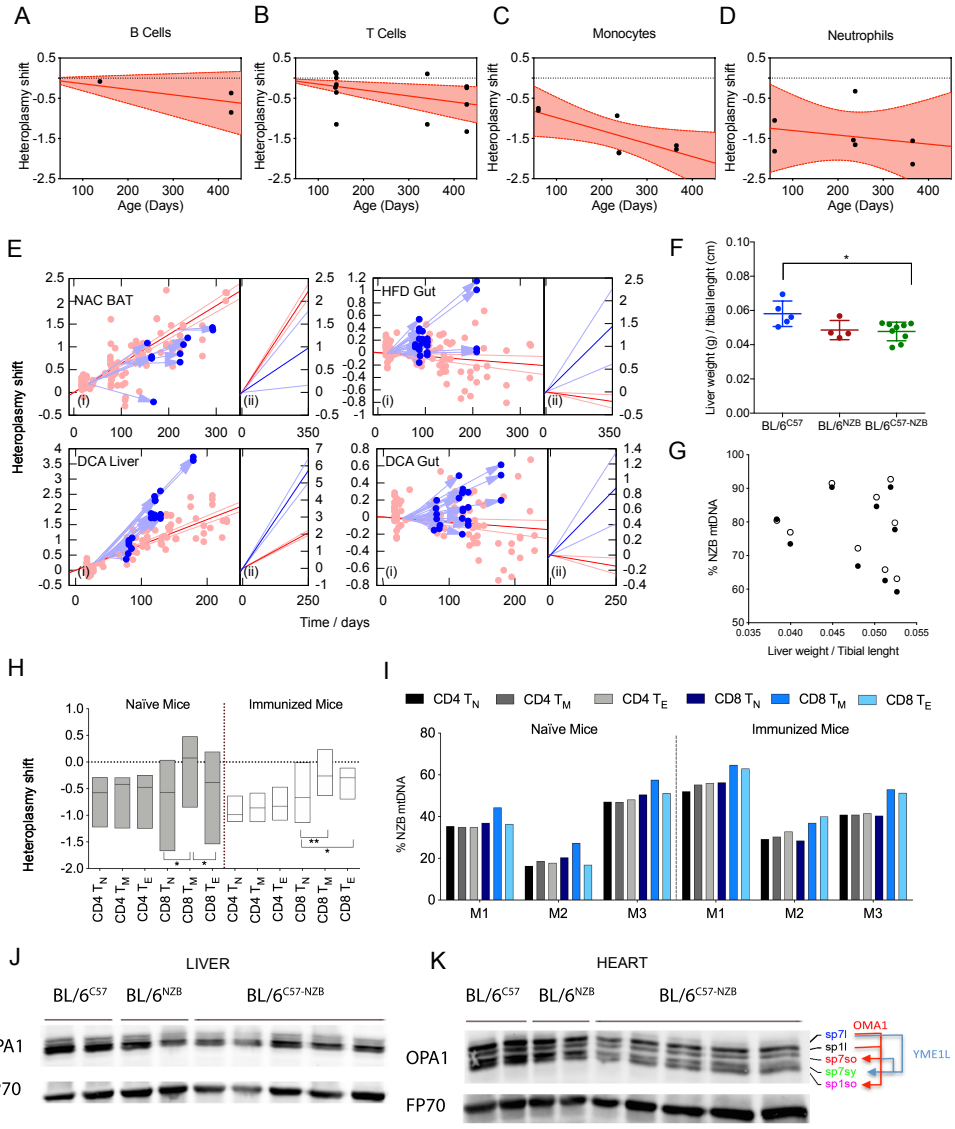

Fig. S2. Evaluation of mtDNA segregation using different environmental interventions. (**A-D**) Transformed heteroplasmy shift using tail as the reference tissue in different cell populations from heteroplasmic mice: B cells (**A**), lymphocytes (**B**), monocytes (**C**) and neutrophils (**D**). Each dot represents a different individual. (**E**) Individual tissues showing a significant difference in segregation with the indicated experimental intervention. Main panels (i): pink points and lines (mean and 95% c.i.s) show the inferred segregation behavior in control mice, relative to eye. Blue vectors show the effects of the indicated experimental treatment (vector starts at treatment onset). Blue points show final heteroplasmy measurements for perturbed mice. Side panels (ii) show the inferred segregation behavior with (blue) and without (pink) treatment, with 95% confidence intervals. (**F**) Weight recovery of the liver after 15 days post-hepatectomy. Each dot corresponds to a different individual. (**G**) Measured percentage of NZB mtDNA in liver before and after hepatectomy (15 days post-surgery). Filled dots are measurements before surgery and empty dots correspond to the amount of NZB mtDNA after liver regeneration. (**H**) Heteroplasmic shift in different CD4+ and CD8+ T cell populations in naïve and immunized mice (n=6 for CD8+ T cells and n=3 for CD4+ T cells). (**I**) Individual mouse analysis of the percentage of NZB mtDNA in T cell subsets in naïve and immunized mice. TN: naïve T cells. TM: memory T cells; TE: effector T cells. M: mouse. (**J, K**) Western blots against OPA1 revealing the distribution between the two isoforms (sp7l and sp1l) and its proteolytic derived forms by either YME1L or OMA1 (see legend) either in liver (**J**) or Heart (**K**) of the different homoplasmic and heteroplasmic mice. Analyses performed in 15-week-old mice. (**A-D**) ** $P < 0.01$ linear regression coefficient and (**F, H**) * $P < 0.05$, ** $P < 0.01$, ANOVA test.

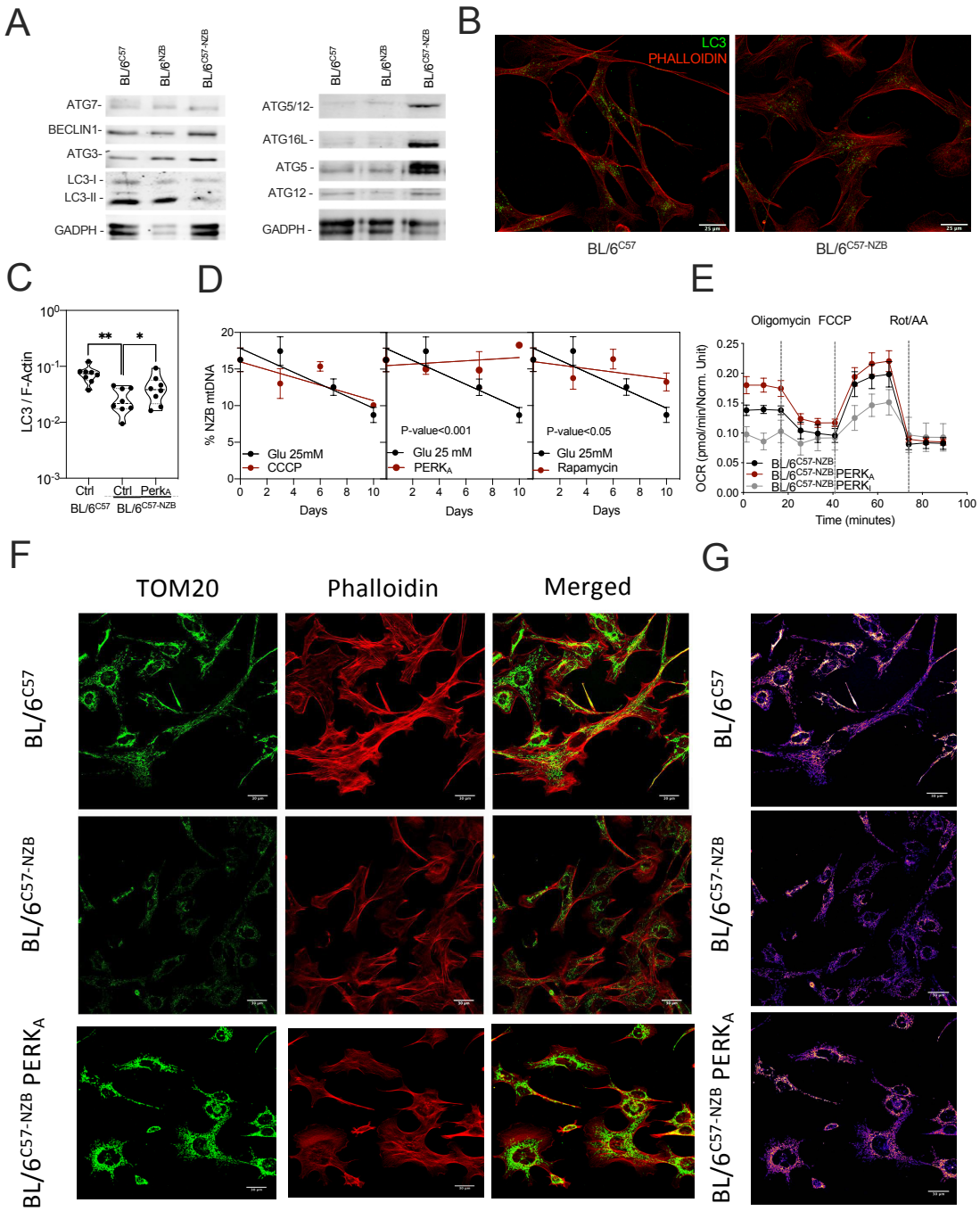

Fig. S3. Confocal imaging analysis of MAF mitochondrial network. (**A**) Autophagy-related proteins analysis by Western Blot in homoplasmic (BL/6C57 and BL/6NZB) and heteroplasmic MAFs (BL/6C57-NZB). Images are representative from two independent experiments. (**B**) Immunofluorescence images of LC3 (green) and phalloidin (F-actin, red) in homoplasmic (BL/6C57) and heteroplasmic (BL/6C57-NZB) MAFs. Scale bar, 25 µm (**C**) Quantification of LC3 levels normalized by the total amount of F-Actin (data obtained from images in b). Violin plot showing all points. Each point represents an individual measure. *P < 0.05, ***P < 0.001, one-way ANOVA with Tukey's multiple comparisons test. (**D**) Modulation of the dynamics of mtDNA segregation in MAFs using different autophagy-related drugs (final concentration 1 µM). Bars show means ± SD, n= 2-3 technical replicates. (**E**) Oxygen consumption rate (OCR) profiles determined by SeaHorseTM in control heteroplasmic MAFs and cells treated for 7 days with PERK

activator (CCT020312, 1μM final concentration) and PERK inhibitor (GSK2606414, 1μM final concentration). Bars show means ± SEM, n=6 technical replicates of each cell clone. **(F-G)** Confocal imaging analysis of MAF mitochondrial networks. **(F)** Confocal imaging of mitochondrial network. TOM20: outer mitochondrial membrane marker in green. Phalloidin: F-actin marker, in red. Scale bar, 30 μm. **(G)** Densitometric image analysis of mitochondrial network distribution within the cells using TOM20 as mitochondrial marker. Purple: low mitochondrial density. Yellow: high mitochondrial density. Scale bar, 30 μm.