**Supplementary Figure legends:**

**Supplementary Fig. S1. Exercise causes a metabolic shift in tissues**. **A,** Hematoxylin and eosin staining (X20 magnification) cross-sections were taken from indicated organs from control mice (top) and active mice (bottom)**.** **B,** Principal component analysis (PCA) plot for proteins taken from the indicated organs of the control and active groups. Scatter plots were created with Perseus software. **C,** Proteomaps of the KEGG pathways enriched in up-regulated proteins in the healthy, routinely active human subjects ( n = 3 males and n = 3 females) following the exercise. **D,** Differential proteins from the mass spec of tissues taken from the control mice were enriched for "GO biological process" (bottom) and "GO cellular compartment" (top) using the GENEONTOLOGY tool. Venn diagrams show the overlap of the GO terms for the indicated organs. **E,** Blood glucose levels were evaluated before and after 16 h of food deprivation for control and active mice (n = 10 mice in control and active groups). **F,** Evaluation of theglycolytic function of single cells originating from the indicated organs using ECAR measurement. Samples were normalized to their *Gapdh* mRNA levels. Error bars represent ± SEM (n ≥ 4). **G,** Oxidative phosphorylation examination of single cells originating from the indicated organs using oxygen consumption rate (OCR) measurement. Samples were normalized to their *Gapdh* mRNA level. Error bars represent ± SEM (n ≥ 4). **H,** qRT-PCR quantification of the mRNAs encoding the indicated mitochondria-specific gene targets from active and control mice. Data were normalized to endogenous levels of *36b4*. Error bars represent ± SEM (n = 4 mice in control and active groups). \* *p* < 0.05; \*\* *p* < 0.01; \*\*\* *p* < 0.001. **I,** FACS analysis of the mitochondrial activity in primary organ cells (lungs, lymph nodes, liver and skeletal muscles) of control and active mice; TMRE expression is indicative of active mitochondria. Representative images of the mean intensity of the FACS data show the TMRE- and TMRE+ cell populations for control and active mice. The X-axis indicates the TMRE intensity and Y-axis indicates the percentage of gated cells.

**Supplementary Fig. 2. High-intensity activities reduce metastatic cancer likelihood. A,** Heatmap showing the differential proteins found in routinely active females serum before versus after treadmill training, generated by the proteomic analysis software Perseus. **B,** Primary lung cells of control and active mice were treated either with vehicle, FCCP (100 µM), or Actinomycin D (800 µM) 60 minutes before co-culturing with GFP-labeled *Ret*-melanoma cells. After 24 hours, FACS analysis of co-culture were performed for TMRE expression, which is an indication of active mitochondria. Mitochondrial activity (active mitochondria - high TMRE and inert mitochondria – low mitochondria) was determined for primary cells (upper panel) and survived melanoma cells (lower panel) demonstrated as (% gated cells) based on the FACS analysis. (n = 4 animals in each group). \* *p* < 0.05; \*\*\* *p* < 0.001**.**

**Supplementary Fig. 3. Exercise inhibits melanoma metastasis formation**. **A,** Upper panel: Representative bright-field (top) and immunofluorescent (bottom) images of *Ret-*melanoma mCherry–Luciferase melanoma cells (left) and primary tumor of subdermally injected mice (right). Tumor images were taken by the CRI Maestro machine. **B,** Luminescence evaluation of lysed *Ret*-melanoma mCherry–Luciferasemelanoma cells. **C,** Whole-animal bioluminescent imaging (left) and photon quantifications (right) of intra-carotid-injected mice that performed exercise only before the melanoma injection and control mice (n = 8 animals in control and active groups). **D,** Schematic representation of exercise-melanoma combined model: the "active" group of mice was trained for 8 weeks using forced treadmill running, and sedentary mice served as control. *Ret*-melanoma mCherry–Luciferase melanoma cells were intra–carotid or -splenic injected to the control and active C57BL/6 mice. After four days of rest, the active mice continued to be trained for up to four weeks, until a metastasis examination was conducted. **E,** Bioluminescence imaging (left) and photon quantifications (right) of melanoma metastases in the lymph nodes and liver of control and active mice. Error bars represent ± SEM. Lymph nodes were taken from intra-carotid-injected mice (n = 10 animals in each group); liver was taken from intra-splenic-injected mice (n = 6 animals in the control and active groups). \* *p* < 0.05; \*\*\* *p* < 0.001. **F,** qRT-PCR of lymph nodes and liver tissues taken from control and active mice. Data were normalized to endogenous controls *Hprt* or *Rplp0* levels. Error bars represent ± SEM (n ≥ 3). \* *p* < 0.05; \*\*\* *p* < 0.001. **G,** Primary cells from indicated organs of control and active mice were co-cultured for 24 hours with *Ret*-melanoma cells (CFSE labeled for proliferation and mcherry labeled for apoptosis) for proliferation (left panel), and apoptosis (right panel). Left panel: For proliferation percentage of CFSE- gated cells are shown for the stroma and melanoma cells. Right panel: For apoptosis percentage of caspase-3+ (apoptotic) and caspase-3- (non-apoptotic) gated cells are shown for the melanoma cells. (n = 4 animals in each group).\**p* < 0.05; \*\*\* *p* < 0.001. **H,** FACS analysis of mitochondrial activity after rapamycin treatment. Primary lung cells were treated with vehicle or rapamycin (100 nM) for 3 hours followed by TMRE staining. Left panel: Representative image of the FACS data shows the TMRE- and TMRE+ cell populations for control and active mice. Middle panel: Quantification (% gated cells) from the FACS for control and active mice. Statistical comparison between TMRE- and TMRE+ from each group (control and active) and TMRE+ between control and active groups is presented in the graphs. (n > 3 animals in each group). ). \*\* *p* < 0.01; \*\*\* *p* < 0.001. Right panel: Representative images of the mean intensity of the FACS data show the TMRE- and TMRE+ cell populations for control and rapamycin-treated lung cells from control mice. The X-axis indicates the TMRE intensity and Y-axis indicates the percentage of gated cells. **I,** FACS analysis of the proliferation of melanoma cells after rapamycin treatment. Primary lung cells were treated with vehicle or rapamycin (100 nM) for 3 hours followed by co-culturing with CFSE labeled *Ret*-melanoma cells. For proliferation percentage of CFSE- gated cells are shown for the melanoma cells. Statistical comparison between control and active from each group (vehicle and rapamycin) and control between (vehicle and rapamycin) is presented in the graphs. (n = 4 animals in each group). ). \* *p* < 0.05; \*\*\* *p* < 0.001.

**Supplementary Fig. 4. Cancer and stroma metabolic crosstalk**. **A,** Heat maps and PCA plots of the normalized expression of genes (rows) of the *in-situ* group (benign nevi, atypical nevi, vertical growth phase melanoma (VGP) and *in-situ* melanoma) compared to metastatic melanoma; the noted disseminated group (lungs to spleen) were created on the basis of genes related to different metabolic pathways (i.e., metabolism, oxygen, energy, hypoxia), as defined by Uniprot. Red- high expression, blue- low expression. **B,** Schematic representation of melanoma and primary cell sorting. Single cells from Lungs, lymph nodes, and, liver tissues from control and active mice were sorted to cancer or stromal cells based on the mCherry red fluorescence of melanoma cells. **C,** qRT-PCR of the metabolic markers *Glut4*, *Aldoa* and *Hspa9* in stroma and tumor originating from lungs, lymph nodes and liver of the control and active mice. Data were normalized to endogenous levels of *36B4*. Error bars represent ± SEM (n=3). \* *p* < 0.05, \*\* *p* < 0.01; \*\*\* *p* < 0.001. **D,** Primary cells from the lungs of control and active mice were co-cultured with *Ret*-melanoma cells (mcherry labelled) in Incucyte® for up to 120 hours. Upper panel: Data represents mean of mCherry+ melanoma cells' intensity for the indicated time points. Lower panel: Representative images of indicated time points and conditions. Error bars represent ± SEM (n = 5 images from each condition and time point). \*\*\* *p* < 0.001 **E,** FACS analysis of the mitochondrial activity in GFP-labeled *Ret*-melanoma cells co-cultured with primary lung cells of control and active mice; TMRE expression is indicative of active mitochondria. Representative images of the mean intensity of the FACS data show the TMRE- and TMRE+ cell populations for lung stroma from control and active mice (upper panel) co-cultured with melanoma cells (lower panel). The X-axis indicates the TMRE intensity and Y-axis indicates the percentage of gated cells.

**Supplementary Fig. 5.** **A-G,** Schematic representation of the experimental models used in this study indicating the experimental design indicated with the related experimental data representation in the figures.