Supplemetary methods

ßCTx ELISA. ßCTx ELISA was obtained from MyBiosource.com (MBS763315) and performed according to manufacturer's instructions.

Na^+ measurements in the skin. After 72 h at 90°C we determined the dry weight (DW) of the samples. We then ashed the tissues at 190° and 450° C for 24 h and at 600° C for 48 h and then dissolved the ashes in 5% HNO^3. We measured Na^+ concentration by atomic adsorption spectrometry (Model 3100, Perkin Elmer, Rodgau, Germany).

Electrolyte and osmolality measurements. Femur bone marrows of 22-weeks-old mice were flushed with a certain amount of H_2O_{dd}. Wet weight of the flushed cells was determined and samples were stored at 4°C until analysis. K^+ was measured by atomic absorption spectrometry after appropriate dilution (Model 3100, Perkin Elmer). Cl^--concentration was assessed by titration with 0.1N silver nitrate (Model Titrando, Metrohm, Filderstadt, Germany). Osmolality of bone marrow was measured using a vapour pressure osmometer (5500 Wescor Inc.) that had been calibrated with appropriate standards.

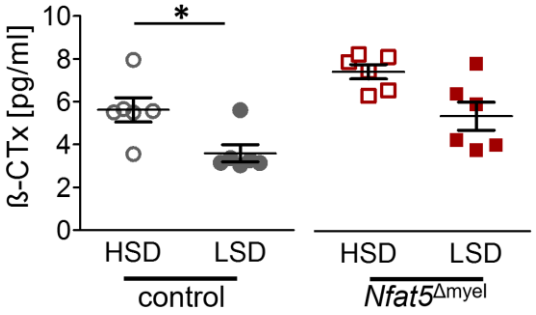
Cultivation of bone-marrow-derived macrophages. Bone marrow (BM) was isolated from the tibia and femur of FVB/N mice by flushing the bone with 10 ml sterile PBS. BM cells were centrifuged for 5 min at 1,400 rpm and erythrocytes were lysed by using 5 ml haemolysis puffer (0.15 M NH_4Cl, 0.01 M $KHCO_3$, 0.1 mM EDTA pH 8.0) for 5 min at room temperature. After that time 10 ml PBS were added and cells were centrifuged for 5 min at 1,400 rpm. Cells were resuspended in 10 mL α-

MEM supplemented with 10% FBS (P30-3306, PAN-Biotech, Aidenbach, Germany), 1% L-glutamine (SH30034.01, GE Healthcare Europe, Munich, Germany), 1% antibiotics/ antimycotics (A5955, Sigma-Aldrich, Munich, Germany) and 30 ng/ ml M-CSF (576404, Biolegend, San Diego, US) and cultivated for 4 h under normal cell culture conditions. After that time, we centrifuged non-adherent cells for 5 min at 1,400 rpm and counted them. Approximately $5x10^6$ cells were seeded on a ø 10 cm cell culture plate and incubated for 4 days in α-MEM (supplemented as described above). After that time BM-derived macrophages were seeded out for experiments in α-MEM (10% FBS, 1%L-glutamine, 1% antibiotics/antimycotics, M-CSF (30 ng/ ml), supplemented with RANK-L (50 ng/ ml, 577102, Biolegend, San Diego, US) for 5 days with or without additional 40 mM NaCl to allow osteoclastogenesis. After that time we analysed gene expression *Nfat5* and osteoclast-specific genes (*Acp5, Ctsk, Mmp9, Oscar*), TRAP in the supernatant and performed CaP resorption assays.

Lactate dehydrogenase (LDH) assay. For cytotoxicity assessment, we performed LDH assays (04744926001, Roche, Mannheim, Germany) using respective cell supernatants of all groups according to the manufacturer's instructions. To determine the maximum releasable LDH activity in the cells (high control) we added 20µl lysis solution to the cells and incubated for 15 min at room temperature. We mixed 100 µl of the supernatant with 100 µl of freshly prepared LDH solution (22 µl catalyst mixed with 1 mL dye) and incubated for 30 min at room temperature in the dark. Then we added 50 µl of stop solution and measured absorbance at 490 nm (LDH activity) with an ELISA reader (Multiscan GO Microplate Spectrophotometer, Thermo Fisher Scientific), subtracting background absorbance at 690 nm.

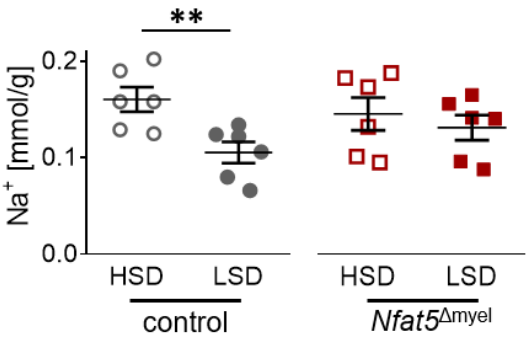
Supplementary Figures

Supplementary Figure 1:



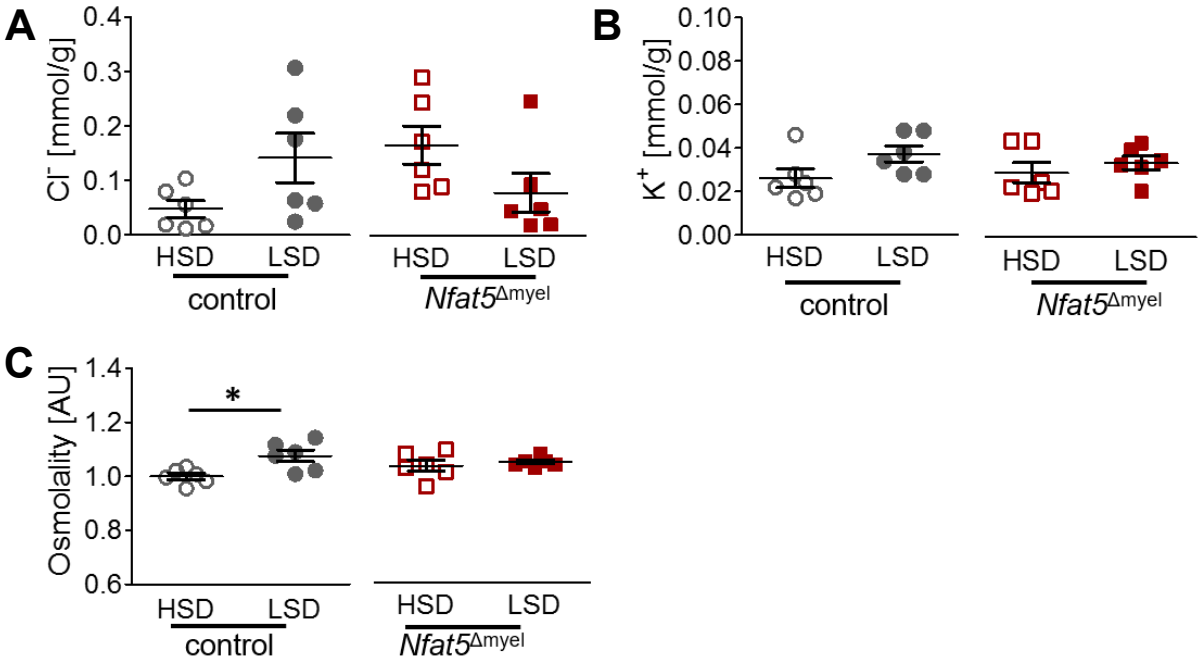
Supplementary Figure 1: ß-CTx levels in serum after HSD or LSD treatment in *Nfat5*$^{\Delta myel}$ mice and littermate controls (n = 6 per group). *p≤0.05. **Statistics:** unpaired, two-tailed Student's t-test.

Supplementary Figure 2:



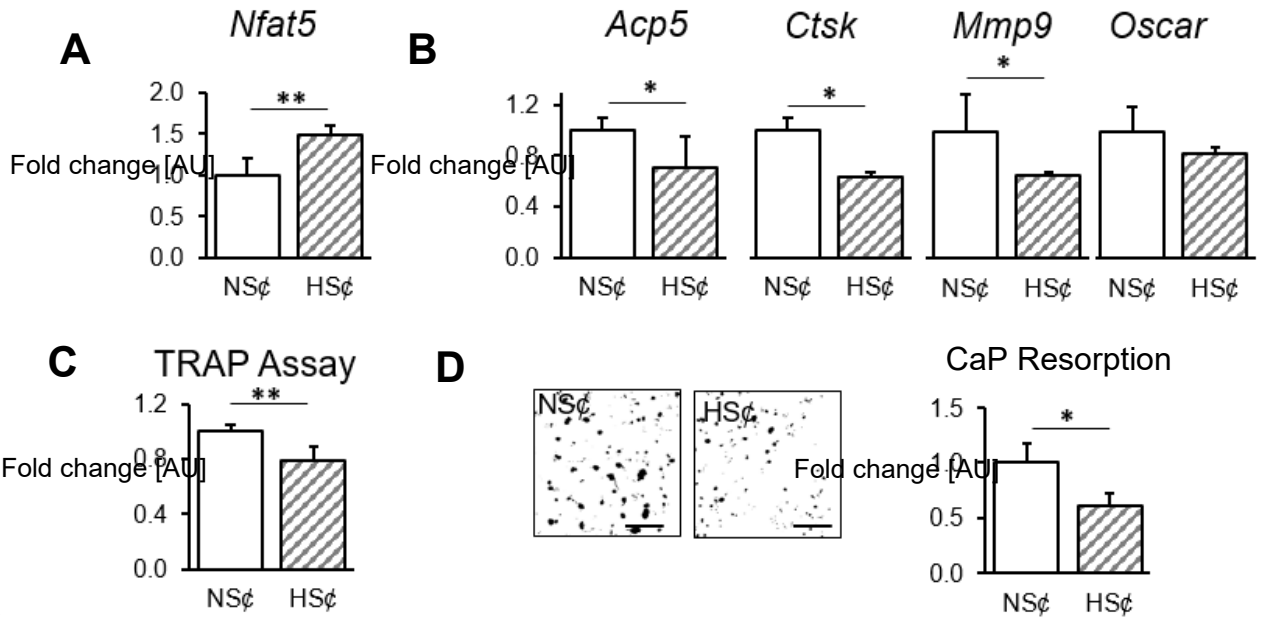
Supplementary Figure 2: Na^+-content in skin after HSD or LSD treatment in *Nfat5*$^{\Delta myel}$ mice and littermate controls (n=6 per group). **p≤0.01. **Statistics:** unpaired, two-tailed Student's t-test.

Supplementary Figure 3:



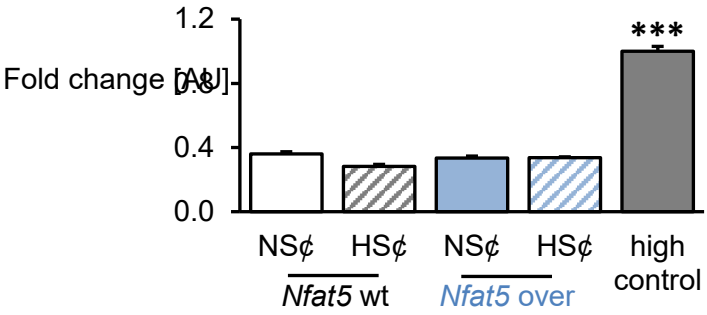
Supplementary Figure 3: Cl^-- **(A)** and K^+-content **(B)** and osmolality **(C)** in bone marrow after HSD or LSD treatment in *Nfat5*$^{\Delta myel}$ mice and littermate controls (n=6 per group). *p≤0.05. **Statistics:** unpaired, two-tailed Student's t-test.

Supplementary Figure 4:



Supplementary Figure 4: High salt (HS¢) prevented osteoclastogenesis of BM-derived macrophages. (A) *Nfat5* mRNA expression under normal salt (NS¢) or HS¢ conditions. **(B)** Expression of osteoclast-specific genes in BM-derived cells after NS¢ or HS¢. **(C)** TRAP assay of the supernatants of indicated samples. **(D)** Representative pictures of CaP resorption assay. Resorbed CaP areas appear as black gaps. Quantification of CaP resorption assay using ImageJ. [AU] arbitrary units; *p≤0.05, **p≤0.01. **Statistics:** unpaired, two-tailed Student's t-tests.

Supplementary Figure 5:



Supplementary Figure 5: High salt conditions revealed no cytotoxic effect on *Nfat5*-wt of *Nfat5*-over cells. To test cytotoxicity of HS¢ we performed LDH assays with cell culture supernatant after 5 d NaCl treatment (n = 6). ***p≤0.001. **Statistics:** Welch-corrected ANOVA with Games-Howell post-hoc-tests.

Supplementary Figure 6:

GTCTGGGTTTGGTGTCTGCGTGTGGGATAGTTCCCCAGGTGGGGCCGTCTCTGGAGGGCCTTTCCTTCAGTCTGT

GTTCCATTCTTTGTCCCCATATTTCCTTTAGACAGAAGCAATTCTGGGTTAAACTTTTGAAGATGGGTGTGTGGT

CCCATCAACTGAGGGGCCATTCCTAACCTCTCGATATGATCTCCACAGGGCATTTCCTATAAAGACCCTCATCAA

TGGAAATGGGTCAGTGGGACAATTGAGGATCTTTTCATCTCAAAGTCCTTAATCTAATTACATCAACAGAGTTCT

CTTTTTTAAATGAAGTAACATGTACATGGTCTCAGGATTATGATATAAATGAAATGATGTGAGGACAACCGACAA

CCCAGTTGATATATCTACCTTCCCGTTACCGCCTTTTCTCTTTTTAAGAGTTAGGTAGTGCAGTTTTCATTTCTT

CCAGTCAGGAGCATAATTTGGTCTTCTGATGTGGTTGGTGTCACTTATAACTTGTTTCATCTATACACCAATCCG

GACTTCAGAAATTCTCCAGTTTCTTATATAGAAAAAACAATCACTTTGGAGATTTTCCTGGCCCACATCTCTTCA

TCTCTAAAAGTTTTTTACAGCGTAGCCCAGGATTTTGTATTTTAAACAACTCCTAGATGTTTGTGGTGATCAAAG

ATGAACAGGCAAACTGTAAGCCAGTAAGCCTAATAATGTCTTGTTCAAATAAAAACAAGAGTAAAAGAAATG

Supplementary Figure 6: *Opg* promotor region with three putative NFAT5 binding sites.