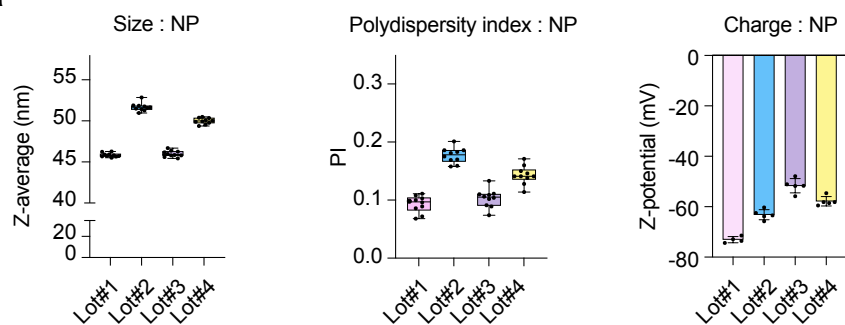


Size-dependent plastic exposure disrupts macrophage function and tissue-specific metabolism

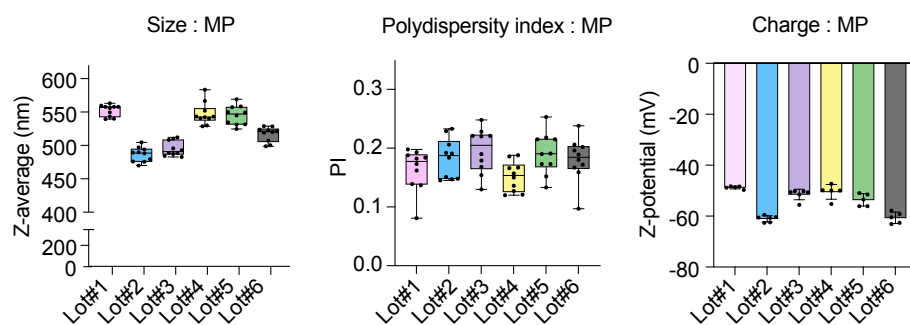
In the format provided by the
authors and unedited

Supplementary Information Figure 1

a



b

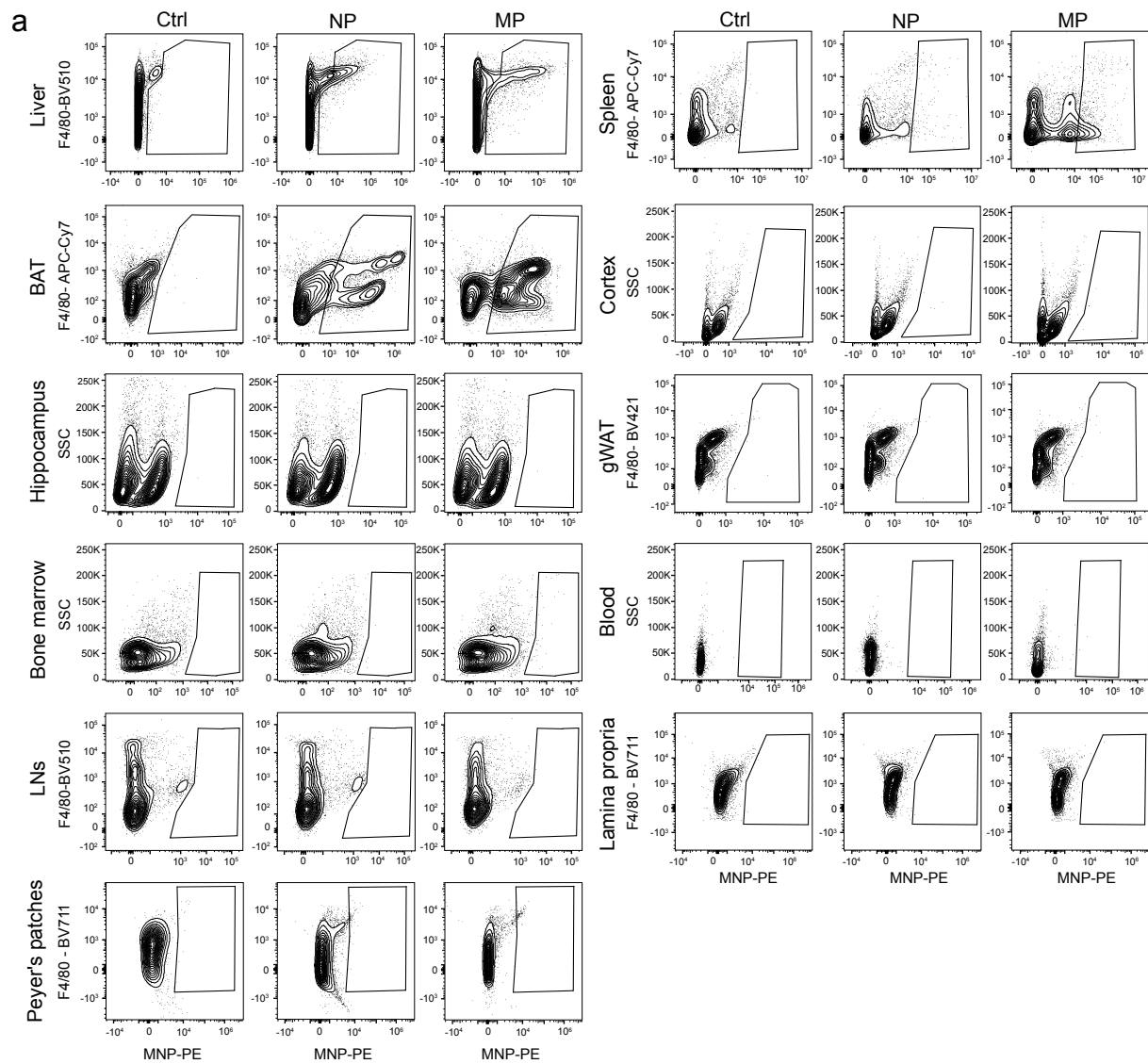


c

	Size		Polydispersity index (PI)		Charge	
	Average (nm)	SD	Average	SD	Average	SD
NP Lot#1	45.8447	0.249528021	0.0931	0.014387108	-73.0645	1.241011013
NP Lot#2	51.6708	0.501358998	0.1768	0.013298287	-63.1688	1.981099367
NP Lot#3	45.9989	0.376762952	0.1029	0.015779382	-51.6676	2.834270418
NP Lot#4	49.9889	0.359123764	0.143	0.01575507	-57.82	1.854718712
MP Lot#1	552.476	8.661359106	0.1637	0.035938373	-48.7746	0.554802037
MP Lot#2	486.3605	10.92735679	0.1826	0.033794148	-61.0438	1.228604642
MP Lot#3	495.0316	11.12022869	0.1959	0.037687163	-51.4778	2.30166433
MP Lot#4	546.9927	16.67798386	0.1518	0.025314906	-50.4738	2.899136371
MP Lot#5	545.0863	14.35607891	0.1913	0.035368065	-53.628	2.430186104
MP Lot#6	517.0394	11.01528925	0.1806	0.037148949	-60.6692	2.231297089

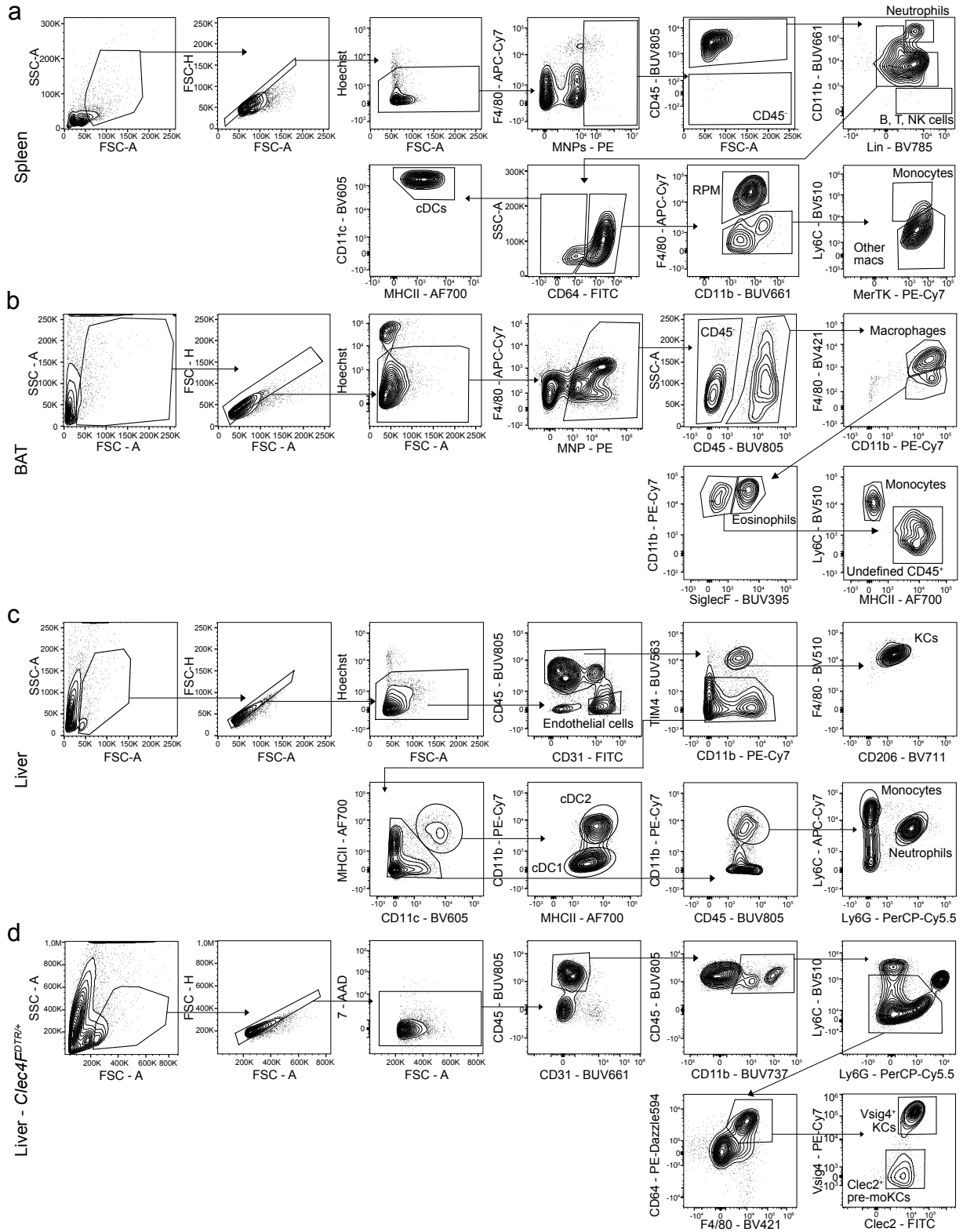
Supplementary information figure 1: Quality control of MNPs. a, Size, polydispersity index (PI) and charge of NP lots used throughout this study. b, Size, polydispersity index (PI) and charge of MP lots used throughout this study. Each dot represents a single measurement. c, Table summarizing the values shown in a and b.

Supplementary Information Figure 2



Supplementary information figure 2: Accumulation of MNPs in organs after chronic MNP treatment. a Representative contour plots showing MNP signal in organs pre-gated on Cells/Single cells/Live, in mice that received 12 weeks of Ctrl, NP or MP 100 mg/kg per week via oral gavage. LN = lymph nodes, BAT = brown adipose tissue, gWAT = gonadal white adipose tissue.

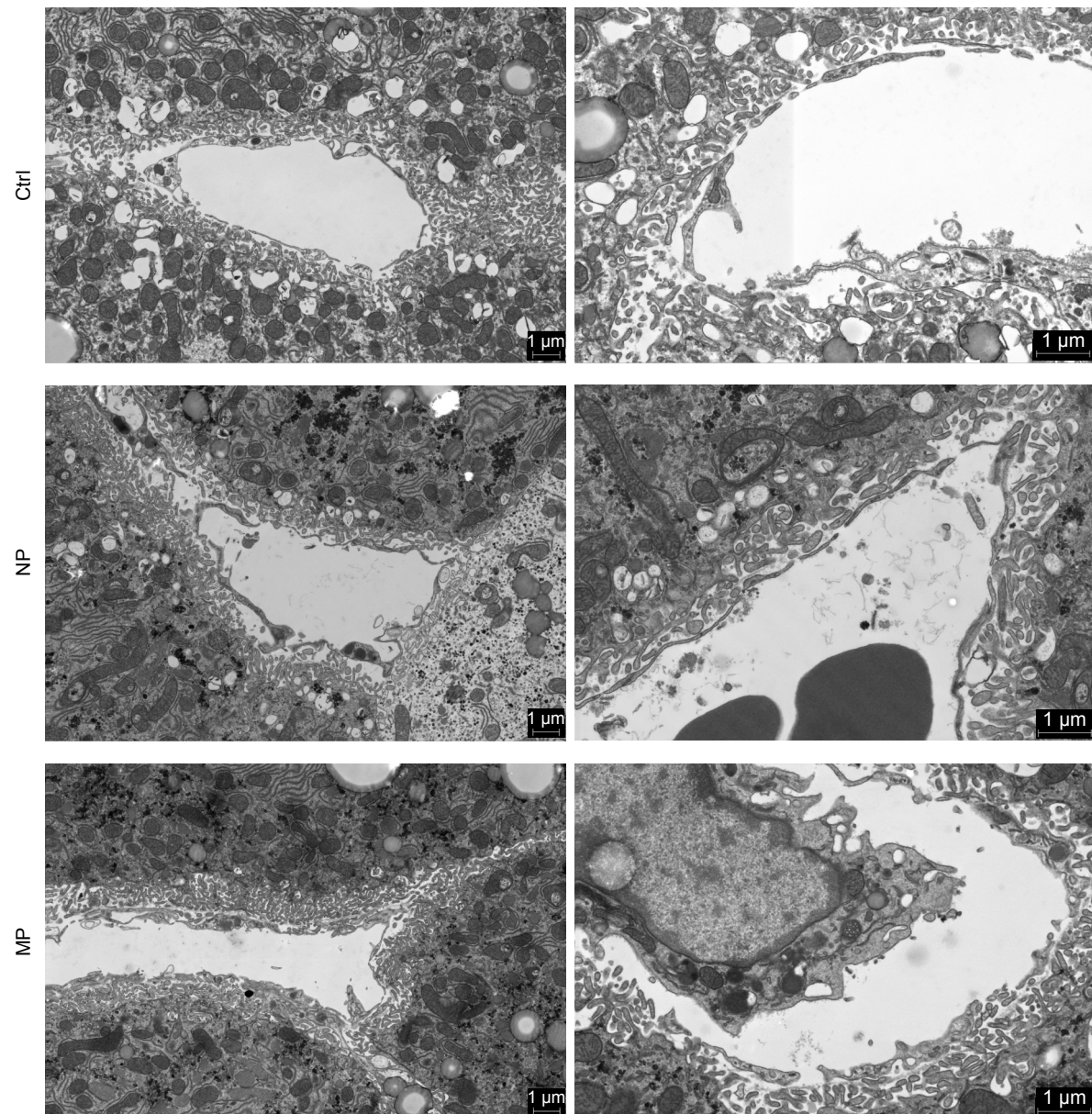
Supplementary Information Figure 3



Supplementary information figure 3: Gating strategy used for flow cytometry data in the spleen, BAT and liver. a, Gating strategy used to identify cells internalising MNPs in the spleen following chronic MNP ingestion as shown in Extended data Figure 2b. Lin = Lineage (CD19, TCR β , Nkp46 and Ly6G), cDC = conventional Dendritic Cells, RPM = red pulp macrophages. **b,** Gating strategy used to identify cells internalising MNPs in the BAT following chronic MNP ingestion as shown in Extended data Figure 2c. **c,** Gating strategy used to quantify cells in the liver as in Figure 1b and Extended Data Figure 9c. KCs = Kupffer Cells, cDC1 = conventional Type 1 Dendritic Cells, cDC2 = conventional Type 2 Dendritic Cells. **d,** Gating strategy used to quantify Vsig4⁺ KCs and Clec2⁺ pre-moKCs in the liver in *Clec4^{EDTR/+}* mice following diphtheria toxin (DT) treatment in Figure 4e, i and Extended data figure 10d-i. pre-moKCs = pre monocyte-derived KCs.

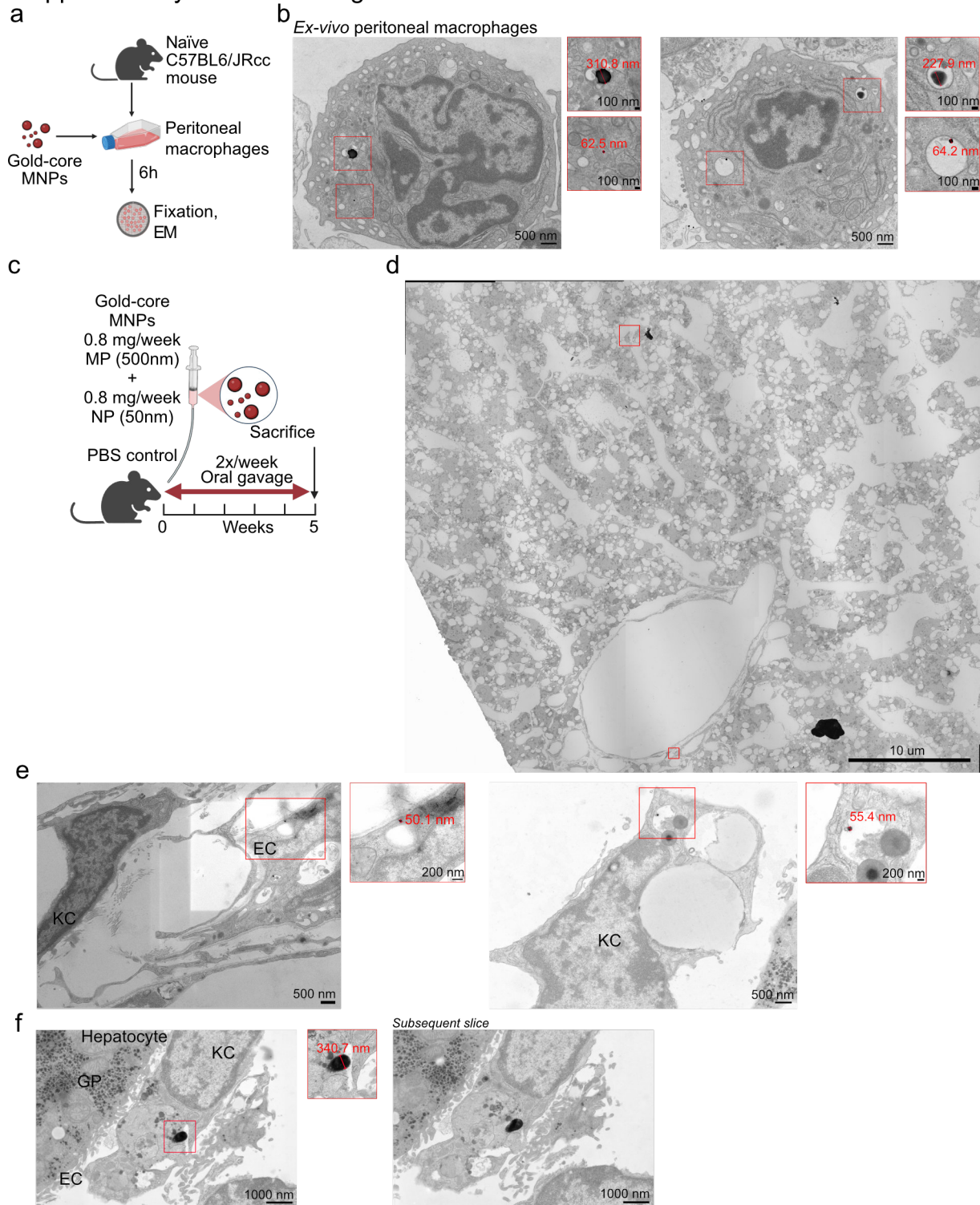
Supplementary Information Figure 4

a



Supplementary information figure 4: Chronic MNP exposure does not impact LSEC fenestration. a, Representative electron microscopy images showing fenestration of liver sinusoidal endothelial cells (LSEC) in mice treated with either Ctrl, NP or MP 100 mg/kg via oral gavage for 12 weeks. Images are representative of $n=2-3$ biological replicates. Scale bars are 1 µm.

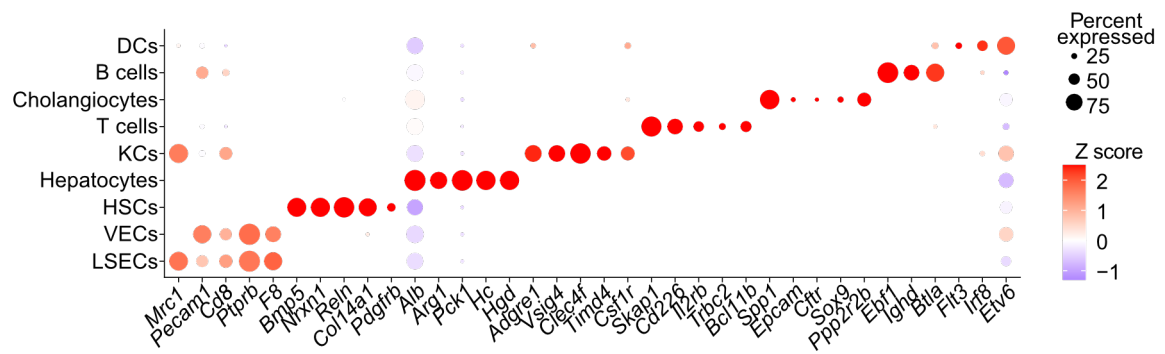
Supplementary Information Figure 5



Supplementary information figure 5: Gold-core MNPs accumulate in KCs and endothelial cells, but not hepatocytes.

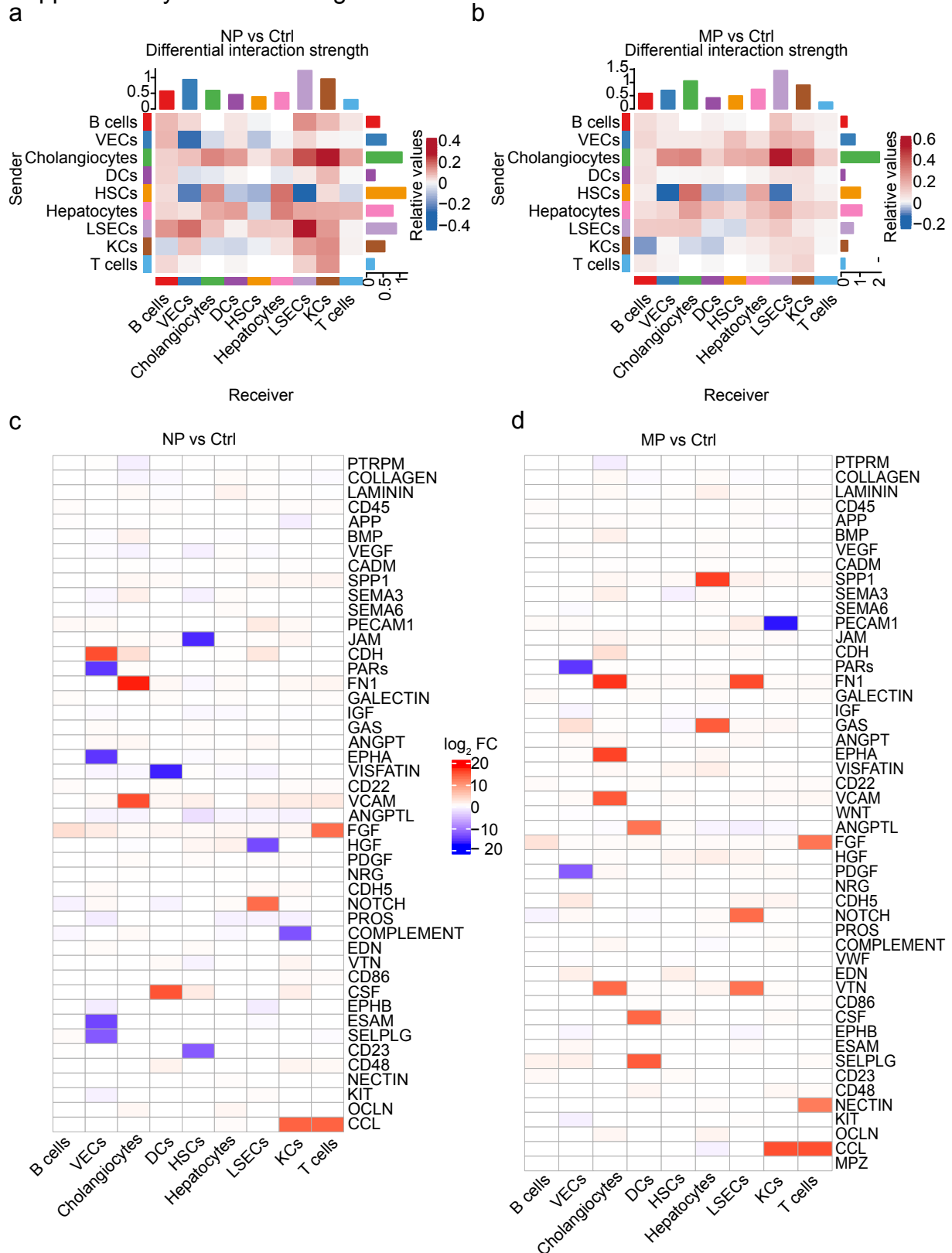
a, Diagram illustrating the generation of cells shown in **b**. Peritoneal macrophages were harvested from a naive mouse and incubated for 6 hours with a mix of gold-core MPs and NPs. After 6 hours, cells were pelleted and fixed for EM analysis. Created in BioRender. <https://BioRender.com/zk4ix8k>. **b**, Electron microscopy images of gold-core MNPs accumulating in peritoneal macrophages, with insets showing measurements of MNPs. **c**, Diagram illustrating the treatment scheme for experiments shown in **d-f** and Fig. 1d. Mice received 0.8 mg/week of each gold-core MP and gold-core NP (gavaged separately, 1 day apart) for 5 weeks, followed by sacrifice and analysis of tissue. Created in BioRender. <https://BioRender.com/1b36jvk>. **d**, Electron microscopy mosaic scan of a liver section of a mouse that received gold-core MNPs as shown in **c**. Red boxes indicate cells that are shown in insets in **c** and **d**. **e**, Electron microscopy images of cells that accumulated MNPs with insets to show MNP size. Cells were identified in the overview shown in **d**. A total of 4 mice were screened. EC = endothelial cell, KC = Kupffer cell, GP = Glycogen particles. **f**, Electron microscopy image of a KC engulfing gold-core MP, shown in two sequential slices to exclude the possibility of artifacts. Scale bars are defined in each image and inset.

Supplementary Information Figure 6



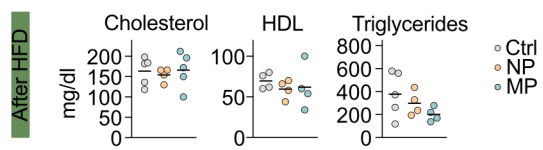
Supplementary information figure 6: Dot plot showing the genes determining the clustering of all cell types determined via single nucleus RNA-seq. DCs = Dendritic Cells, KCs = Kupffer Cells, HSCs = Hepatic stellate cells, VECs = Vascular Endothelial cells, LSECs = Liver Sinusoidal Endothelial Cells.

Supplementary Information Figure 7



Supplementary information figure 7: Changes in cellular crosstalk following chronic NP or MP exposure. a,b, Global differences in cell-cell interaction strength in NP-treated (a) and MP-treated (b) mice compared to Ctrl-treated mice, inferred from single-nucleus RNA-seq data. Heatmaps depict the relative change in total interaction strength between sender (rows) and receiver (columns) cell types. VECs = Vascular endothelial cells, DCs = Dendritic cells, HSCs = Hepatic stellate cells, HSCs = Hepatic stellate cells, KCs = Kupffer cells. **c, d,** Pathway-level changes in intercellular signaling in NP-treated (c) and MP-treated (d) mice compared to Ctrl. For each pathway and cell type, total signaling strength was calculated as the sum of outgoing and incoming interactions, and $\log_2$ fold changes were computed between treatment and control conditions.

Supplementary Information Figure 8



Supplementary information figure 8: Total cholesterol, high-density lipoproteins (HDL) and triglycerides measured in the serum of mice after chronic plastic feeding in combination with high-fat diet. $n= 5$ (Ctrl), $n= 4$ (NP), $n= 5$ (MP) biological replicates.

Source data Supplementary Information figure 8
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	Cholesterol		
	Ctrl	NP	MP
Biological replicate 1	182	166	172
Biological replicate 2	136	154	150
Biological replicate 3	118	166	212
Biological replicate 4	198	130	196
Biological replicate 5	184		100

	HDL		
	Ctrl	NP	MP
Biological replicate 1	62	58	60
Biological replicate 2	76	70	54
Biological replicate 3	60	66	100
Biological replicate 4	80	44	34

	Triglycerides		
	Ctrl	NP	MP
Biological replicate 1	578	436	218
Biological replicate 2	118	236	278
Biological replicate 3	560	328	138
Biological replicate 4	262	194	170
Biological replicate 5	372		