

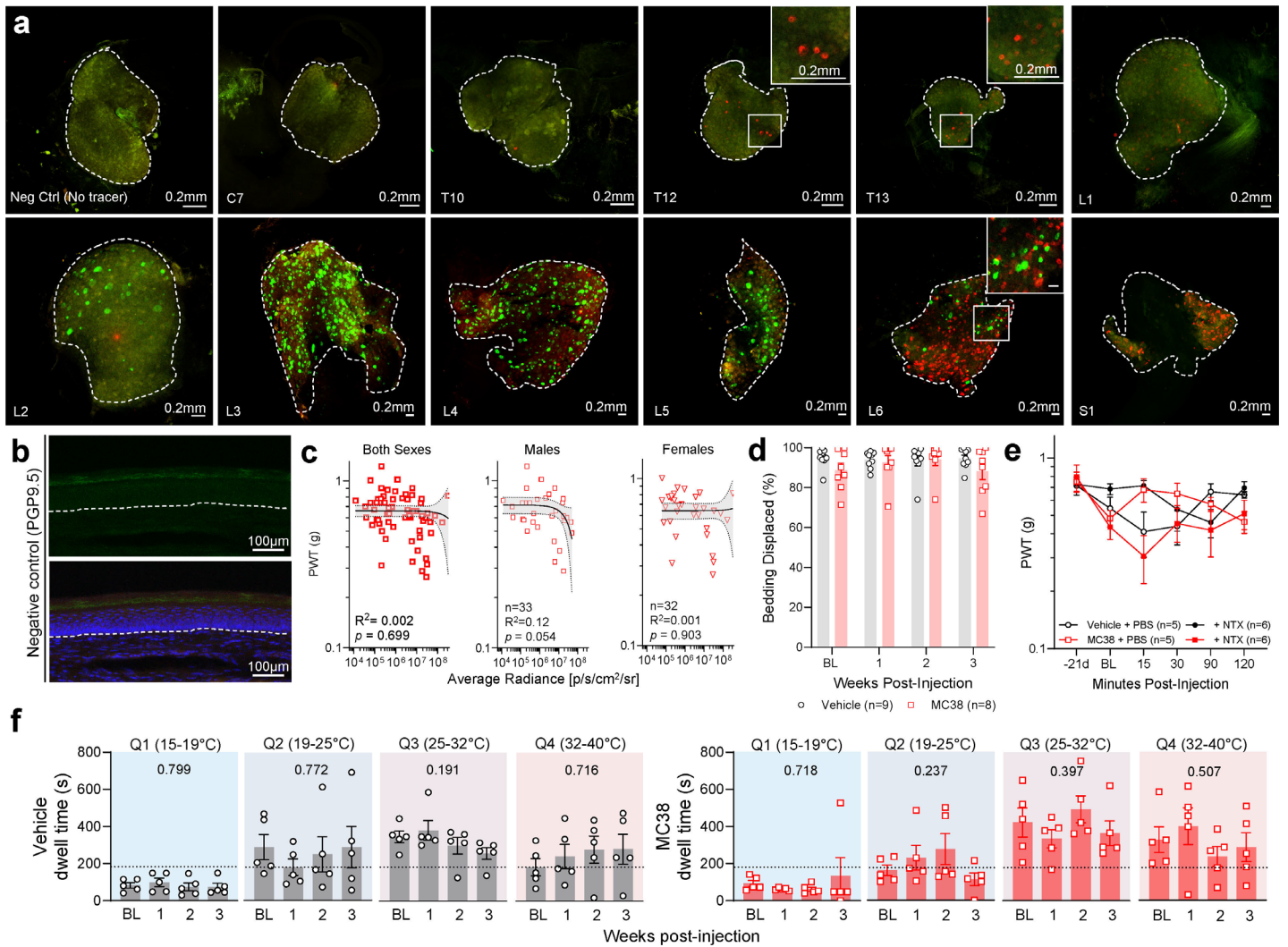
Supplementary Information For:

Inflammatory Neuropathy in Mouse and Primate Models of Colorectal Cancer

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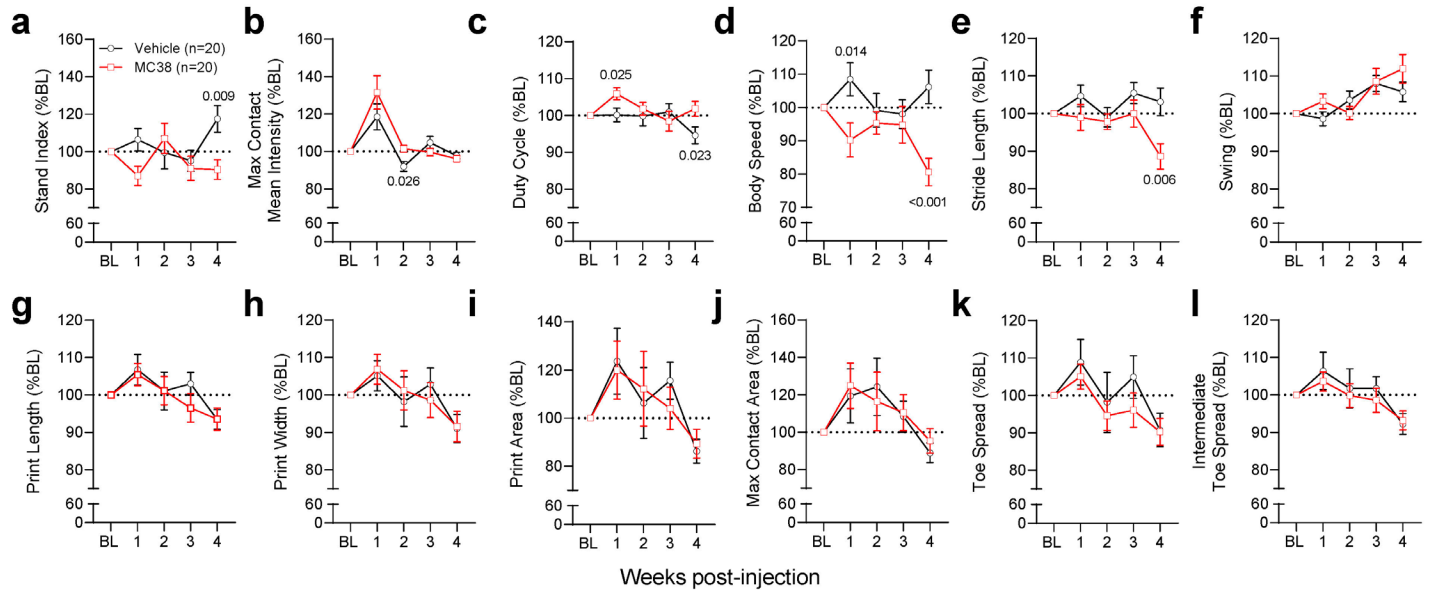
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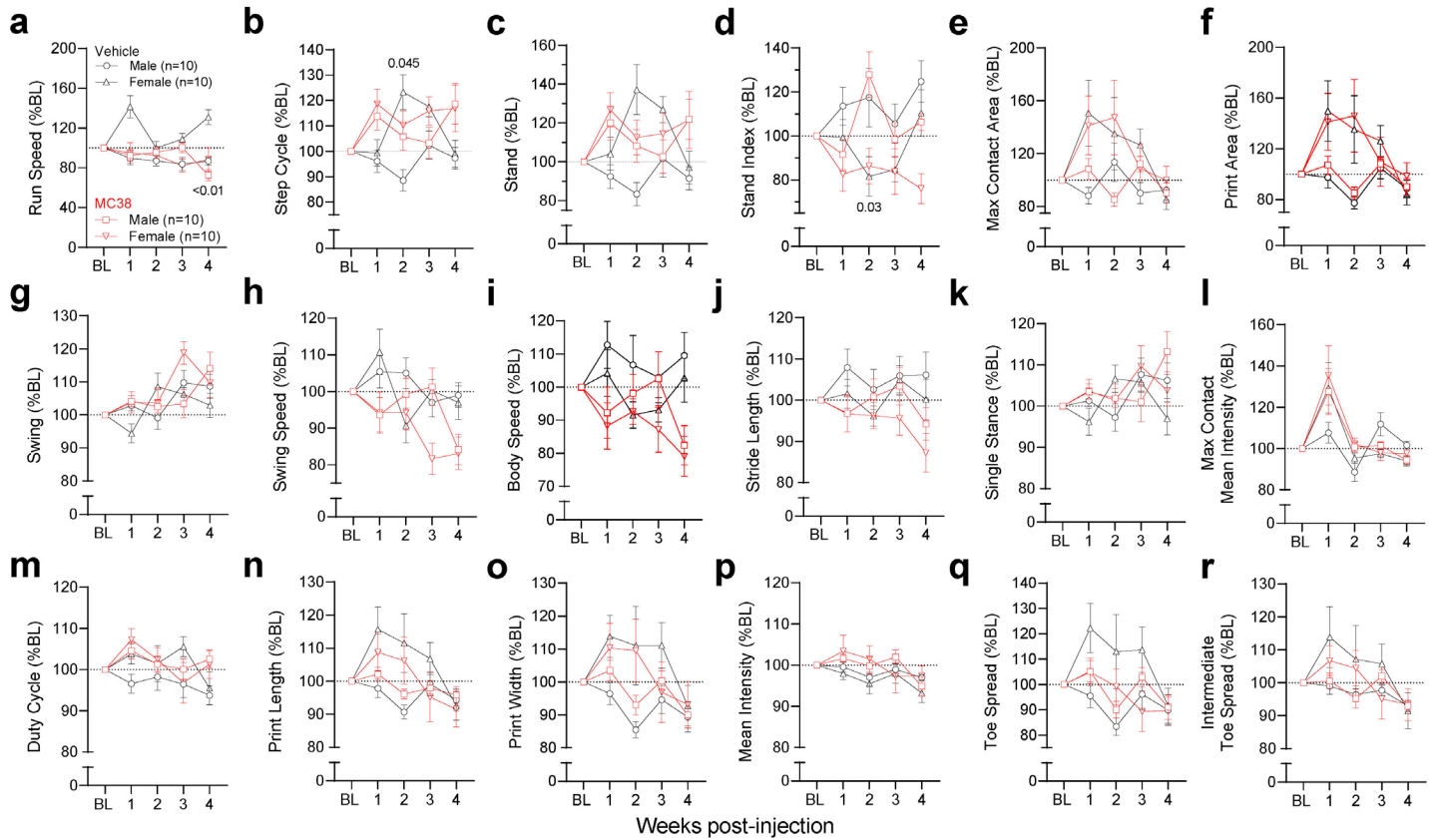
Supplementary Figure 1. Effect of MC38 tumor growth on neuropathy and sensory sensitivity.

(a) Whole-mount DRG labeling of afferents innervating hind paw (green) and distal colon/rectum (red). Hindpaw innervation is chiefly restricted to L3-L5, with colon innervation emanating from lower thoracic (T12-T13) and lower lumbar/sacral levels (L6/S1). Dual-labeled afferents were not observed. Scale bars = 0.2mm. (b) Negative control image for PGP9.5 IHC of plantar skin. (c) No significant correlation between mean paw withdrawal threshold (PWT) value and tumor luminescence intensity in both sexes ($F_{1,63}=0.151$, $p=0.699$) or female MC38 mice ($F_{1,30}=0.015$, $p=0.903$), with a borderline effect in males ($F_{1,31}=4.025$, $p=0.054$). Trendline = linear regression; shaded area = 95% confidence interval. Scale bars = 100µm. (d) Burrowing activity does not significantly differ between vehicle-injected and MC38-injected mice ($F_{1,15}=1.505$, $p=0.239$; two-sided two-way ANOVA). (e) Three weeks post-vehicle or MC38 injection, mice received subcutaneous vehicle (PBS) or naltrexone (NTX, 3 mg/kg) to unmask any latent pain hypersensitivity. There was a significant main effect of time post-injection ($F_{3.3,59.4}=4.504$, $p=0.005$), a significant tumor x treatment interaction ($F_{1,18}=6.368$, $p=0.021$) and a significant time x tumor type x drug interaction ($F_{3.3,59.4}=2.895$, $p=0.038$). Fifteen minutes post-injection, MC38 mice treated with NTX were not significantly more sensitive than MC38 mice that received PBS ($p=0.467$). Two-sided, three-way repeated measures ANOVA, Dunnett's multiple comparisons test. (f) Vehicle control mice (left, grey) display a consistent aversion to the coolest quadrant of the thermal gradient ring (Q1; 15-19°C), with the strongest, most consistent preference for Q3 (25-32°C). MC38 mice (right, red) exhibit a broadly similar temperature preference pattern. No main effect of timepoint on temperature preference (Q1 vehicle/MC38: $F_{3,16}=0.337/0.454$,

$p=0.799/0.718$; Q2 vehicle/MC38: $F_{3, 16}=0.375/1.563$, $p=0.772/0.237$; Q3 vehicle/MC38: $F_{3, 16}=1.781/1.051$, $p=0.191/0.397$; Q4 vehicle/MC38: $F_{3, 16}=0.457/0.809$, $p=0.716/0.507$). Two-sided one-way ANOVA. Dotted line represents predicted dwell time in the absence of preference (i.e. $750/4 = 187.5$ seconds). Source data are provided as a Source Data file.

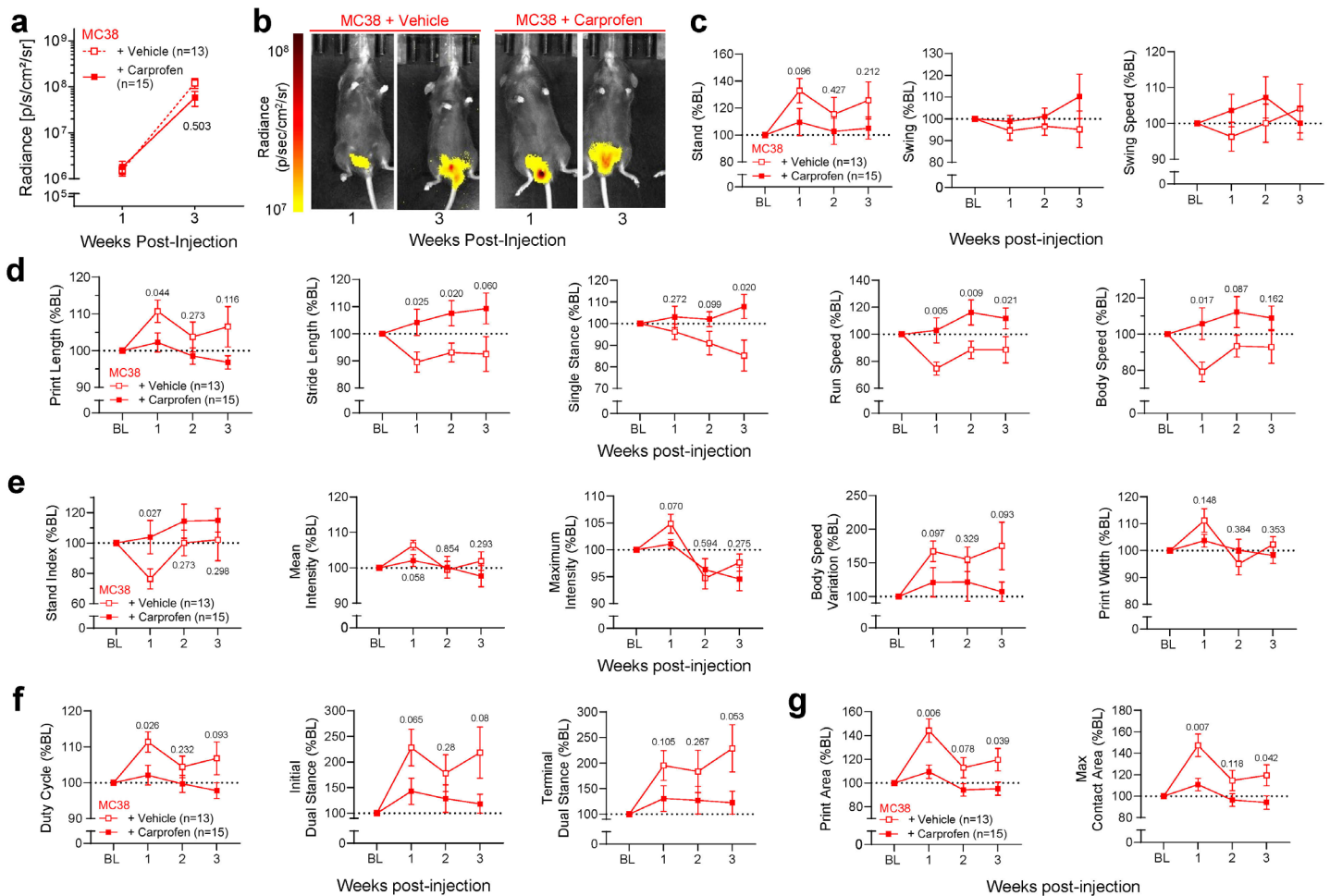


Supplementary Figure 2. Effect of MC38 tumor growth on gait. (a) Stand index (speed of propulsion phase): significant time x tumor interaction ($F_{4, 151}=4.692$, $p=0.001$), with a significant increase in vehicle mice at week 4 ($t(189)=3.176$, $p=0.009$). (b) Max contact mean intensity: main effect of time ($F_{1.49, 56.26}=19.66$, $p<0.0001$), with a significant decrease in vehicle mice at week 2 ($t(33.74)=2.992$, $p=0.026$). (c) Duty cycle (proportion of a step cycle spent in stand vs swing phase): main effect of time ($F_{3.374, 127.4}=2.665$, $p=0.044$) and a time x tumor interaction ($F_{4, 151}=3.499$, $p=0.009$), with significant differences at weeks 1 and 4 ($t(37.52)=3.305$, $p=0.025$ [week 1]; $t(36.76)=3.363$, $p=0.023$ [week 4]). (d) Body speed (distance traveled in the time taken per step cycle): main effect of tumor ($F_{1, 38}=6.164$, $p=0.018$) and a time x tumor interaction ($F_{4, 151}=5.292$, $p=0.0005$), with significant differences at weeks 1 and 4 ($t(37.97)=3.627$, $p=0.014$ [week 1]; $t(36.03)=5.559$, $p=0.0004$ [week 4]). (e) Stride length: main effect of time ($F_{3.305, 114.8}=3.202$, $p=0.022$) and a time x tumor interaction ($F_{4, 151}=3.461$, $p=0.0099$), with a significant difference at week 4 ($t(33.97)=4.117$, $p=0.006$). (f) Swing: main effect of time ($F_{2.972, 103.3}=8.253$, $p<0.0001$). (g-l) Print length/ print width/ print area / max contact area / toe spread (first and fifth digit)/ intermediate toe spread (second and fourth digit): main effect of time ($F_{(2.438, 92.02)}=7.694$, $p=0.0003$ [print length]; $F_{2.378, 89.76}=6.969$, $p=0.0008$ [print width]; $F_{1.823, 63.35}=5.539$, $p=0.008$ [print area]; $F_{2.065, 77.96}=5.518$, $p=0.005$ [max contact area]; $F_{2.603, 98.27}=6.769$, $p=0.0006$ [toe spread]; $F_{2.493, 94.12}=7.343$, $p=0.0004$ [intermediate toe spread]). Two-sided two-way mixed-effects analysis, Šídák's multiple comparisons test. Error bars = SEM. Source data are provided as a Source Data file.



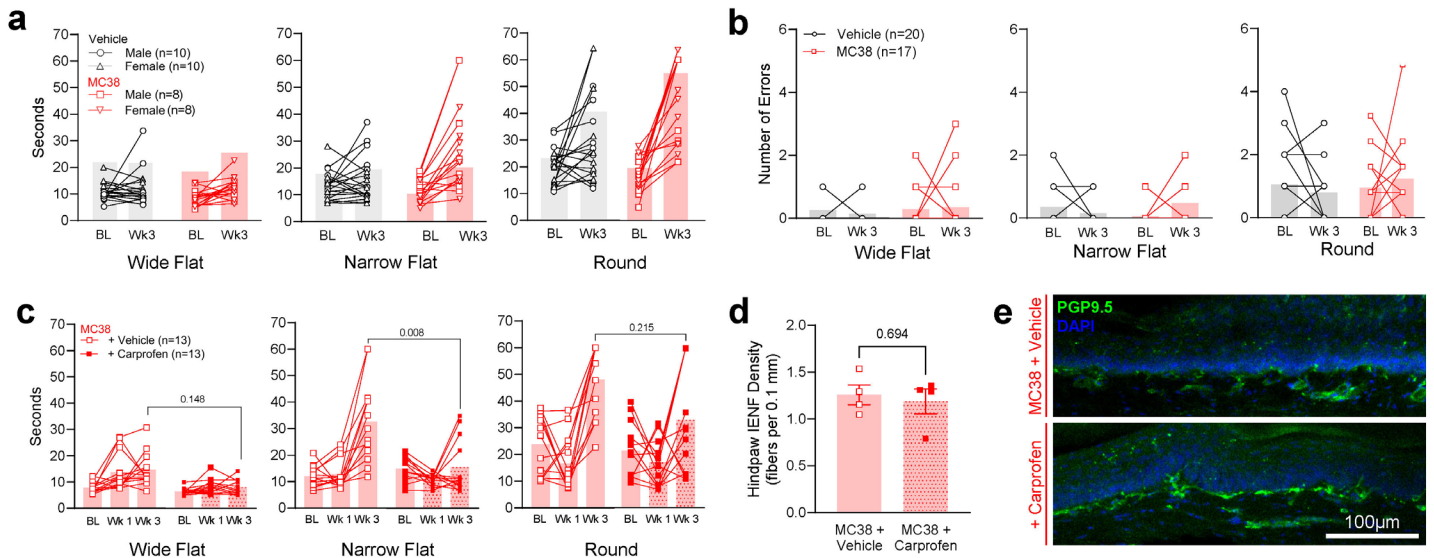
Supplementary Figure 3. Gait analysis of male and female vehicle and MC38 mice. (a) Run speed: main effects (sex: $F_{1,36}=8.894$, $p=0.005$, time: $F_{2,831,101.9}=8.894$, $p=0.024$, tumor: $F_{1,36}=6.081$, $p=0.019$). Significant time/sex ($F_{4,144}=7.455$, $p<0.0001$), time/tumor ($F_{4,144}=6.517$, $p<0.0001$), sex/tumor ($F_{1,36}=9.685$, $p=0.004$), and time/sex/tumor interactions ($F_{4,144}=3.741$, $p=0.006$). Significant difference: vehicle male vs vehicle female, week 4 ($p=0.0096$). (b) Step cycle: main effects (sex: $F_{1,36}=4.921$, $p=0.033$, time: $F_{2,831,101.9}=3.015$, $p=0.032$, tumor: $F_{1,36}=5.444$, $p=0.025$); significant time/sex ($F_{4,143}=4.239$, $p=0.003$) and time/tumor interactions ($F_{4,143}=5.567$, $p=0.0003$). Significant difference: vehicle male vs vehicle female, week 2 ($p=0.045$). (c) Stand: main effect (sex: $F_{1,36}=4.509$, $p=0.041$); significant time/sex ($F_{3,124,111.7}=3.142$, $p=0.0264$), and time/tumor interactions ($F_{3,124,111.7}=5.323$, $p=0.002$). (d) Stand index: main effect (sex: $F_{1,36}=10.85$, $p=0.002$), with significant time/sex ($F_{4,143}=5.188$, $p=0.0006$), and time/tumor interactions ($F_{4,143}=5.034$, $p=0.0008$). Significant difference: male vs female MC38 mice, week 2 ($p=0.03$). (e) Max contact area: main effects (sex: $F_{1,36}=4.144$, $p=0.049$, time: $F_{2,013,71.97}=6.254$, $p=0.031$), and their interaction ($F_{2,013,71.97}=4.674$, $p=0.012$). (f) Print area: main effects (time: $F_{1,95,69.7}=6.863$, $p=0.002$), sex: $F_{1,36}=5.026$, $p=0.031$), and their interaction ($F_{1,95,69.7}=7.462$, $p=0.001$). (g) Swing: main effect (time: $F_{2,888,103.3}=9.332$, $p<0.0001$), and significant time/sex ($F_{4,143}=3.262$, $p=0.014$), and time/sex/tumor interactions ($F_{4,143}=3.161$, $p=0.016$). (h) Swing speed: main effects (time: $F_{3,376,120.7}=5.895$, $p=0.0005$, tumor: $F_{1,36}=7.432$, $p=0.0098$); significant time/sex ($F_{3,376,120.7}=2.601$, $p=0.049$), time/tumor ($F_{3,376,120.7}=4.173$, $p=0.006$), and time/sex/tumor interactions ($F_{3,376,120.7}=3.166$, $p=0.022$). (i) Body speed: main effect (tumor: $F_{1,36}=6.318$, $p=0.017$) and a time/tumor interaction ($F_{3,374,120.6}=5.21$, $p=0.0013$). (j) Stride length: main effect (tumor: $F_{1,36}=4.413$, $p=0.043$) and a time/tumor interaction ($F_{3,405,121.7}=2.83$, $p=0.035$). (k) Single stance: main effect (time: $F_{3,132,112}=3.213$, $p=0.024$), and a time/sex interaction ($F_{3,132,112}=3.478$, $p=0.017$). (l) Max contact mean intensity: main effect (time: $F_{1,44,51.47}=20.66$, $p<0.0001$). (m) Duty cycle: main effect (time: $F_{3,316,118.6}=2.657$, $p=0.046$), and a time/tumor interaction ($F_{3,316,118.6}=3.525$, $p=0.014$). (n) Print length: main effect (time: $F_{2,653,94.84}=8.76$, $p<0.0001$), and a

time/sex interaction ($F_{2.653,94.84}=7.13$, $p=0.0004$). (o) Print width: main effect (time: $F_{2.474,88.44}=7.67$, $p=0.0003$), and a time/sex interaction ($F_{2.474,88.44}=4.637$, $p=0.008$). (p) Mean intensity: main effect (time: $F_{3.153,112.7}=5.407$, $p=0.001$). (q) Toe spread: main effect (time: $F_{2.724,97.37}=7.606$, $p=0.0002$), and a time/sex interaction ($F_{2.724,97.37}=4.049$, $p=0.012$). (r) Intermediate toe spread: main effect (time: $F_{2.512,89.81}=7.783$, $p=0.0003$) and a time/sex interaction ($F_{2.512,89.81}=3.14$, $p=0.037$). Error bars = SEM. Two-sided three-way ANOVA/mixed effects analysis, Tukey's multiple comparisons test. Source data are provided as a Source Data file.

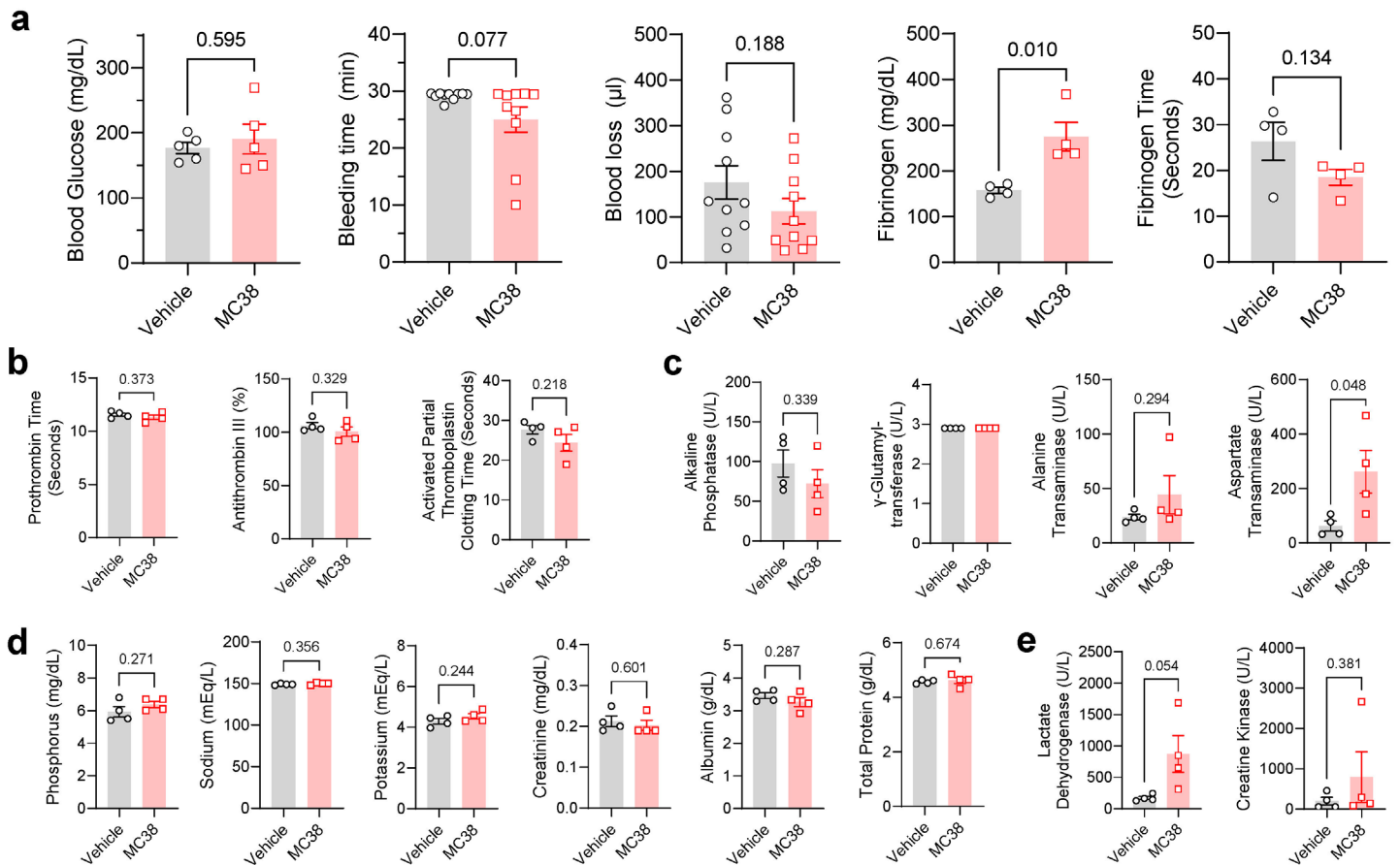


Supplementary Figure 4. Effect of carprofen on gait performance. (a-b) Carprofen treatment does not significantly alter MC38 tumor burden. (c) Gait analysis of MC38 mice with and without carprofen treatment, no significant main effect for stand time, swing time or swing speed. (d) Significant main effects of carprofen for: print length ($F_{1,26}=4.623$, $p=0.041$), with a significant difference at week 1 ($p=0.044$); stride length ($F_{1,26}=8.955$, $p=0.006$), with significant differences at weeks 1 and 2 ($p=0.025$ and 0.02 , respectively); single stance time ($F_{1,26}=7.443$, $p=0.011$), with a significant difference at week 3 ($p=0.02$); run speed ($F_{1,26}=9.287$, $p=0.005$), with significant differences at weeks 1, 2, and 3 ($p=0.017$, 0.087 and 0.021 , respectively); and body speed ($F_{1,26}=6.569$, $p=0.017$), with a significant difference at week 1 ($p=0.017$). (e) a significant main effect of time was found for: stand index ($F_{3,77}=2.772$, $p=0.047$), with a significant difference at week 1 ($p=0.027$); mean hindpaw intensity ($F_{2,16,55.5}=3.16$, $p=0.047$); maximum hindpaw intensity ($F_{2,291,58.81}=12.85$, $p<0.0001$); body speed variation ($F_{2,805,71.99}=3.243$, $p=0.03$); and print width ($F_{2,494,64.01}=6.253$, $p=0.002$). (f) Significant main effects of time and carprofen treatment were found

for: duty cycle ($F_{2,721,69.83}=3.06$, $p=0.038$ [time], $F_{1,26}=5.952$, $p=0.022$ [carprofen]), with a significant difference at week 1 ($p=0.026$); initial dual stance ($F_{2,77,71.08}=4.921$, $p=0.005$ [time], $F_{1,26}=4.543$, $p=0.043$ [carprofen]); and terminal dual stance ($F_{2,773,71.23}=4.053$, $p=0.012$ [time], $F_{1,26}=4.507$, $p=0.043$ [carprofen]). (g) A significant time/carprofen interaction was found for: print area ($F_{2,075,53.25}=3.143$, $p=0.039$), with significant differences at weeks 1 and 3 ($p=0.006$ and 0.039 , respectively); and area at maximum contact ($F_{2,202,56.52}=3.354$, $p=0.038$), with significant differences at weeks 1 and 3 ($p=0.007$ and 0.042 , respectively). Error bars = SEM. Two-sided mixed effects analysis, Tukey's multiple comparisons test. Source data are provided as a Source Data file.

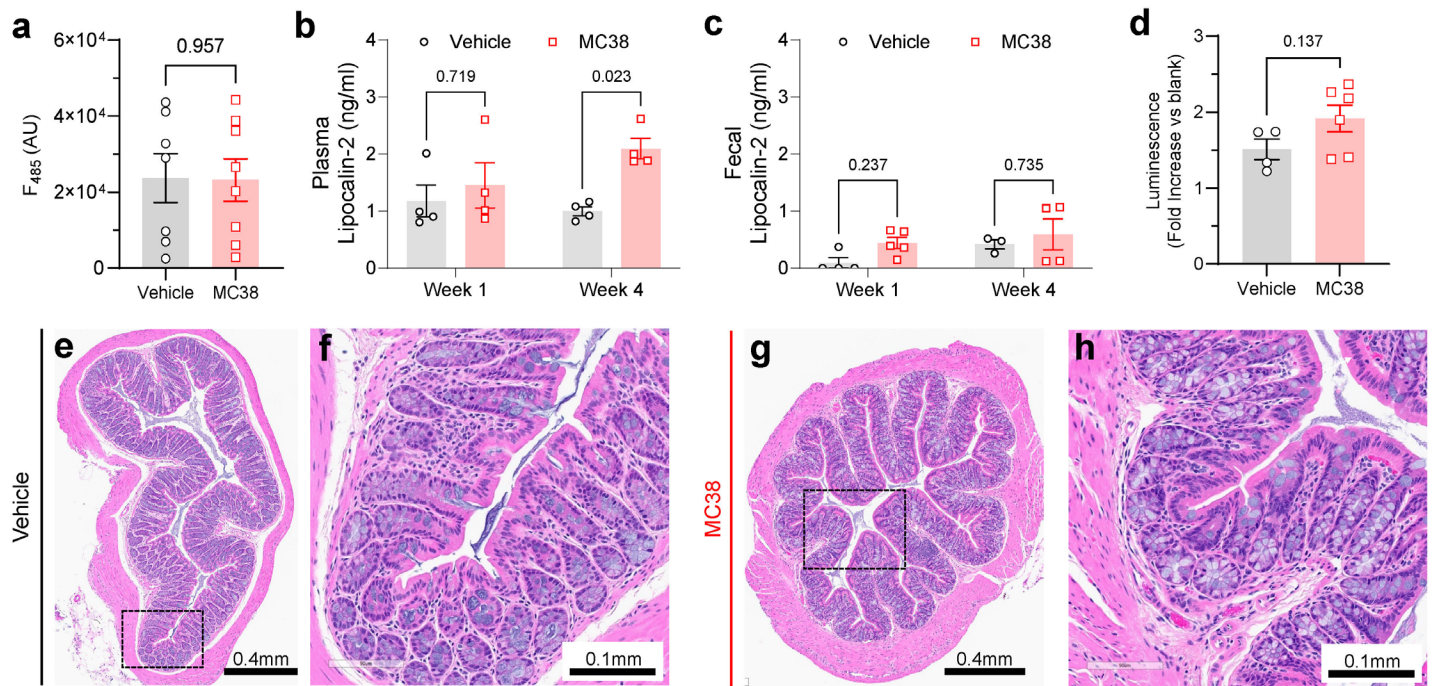


Supplementary Figure 5. Beam walk performance and effect of carprofen. (a) Male and female MC38 mice show similar deterioration in beam walk performance. (b) Number of errors (paw slips, inversions, falls) in the beam walk task. Absolute error number increases in the narrow flat and round beams versus the wide flat beam in vehicle controls and MC38 mice. (c) Deficits in MC38 mouse beam walk performance are attenuated by carprofen treatment. At week 3, the time taken for carprofen-treated mice to complete a cross was significantly shorter for the narrow flat beam ($t(72) = 3.129$, $p = 0.008$), but not the wide flat or rounded beam. Aligned rank-transformed one-way ANOVA, Šidák's multiple comparisons test. (d-e) No statistically significant difference in hindpaw IENF density in MC38 mice treated with carprofen versus vehicle ($t(6) = 0.413$, $p = 0.694$, two-sided unpaired T test). Scale bar = 100µm. Error bars = SEM. Source data are provided as a Source Data file.



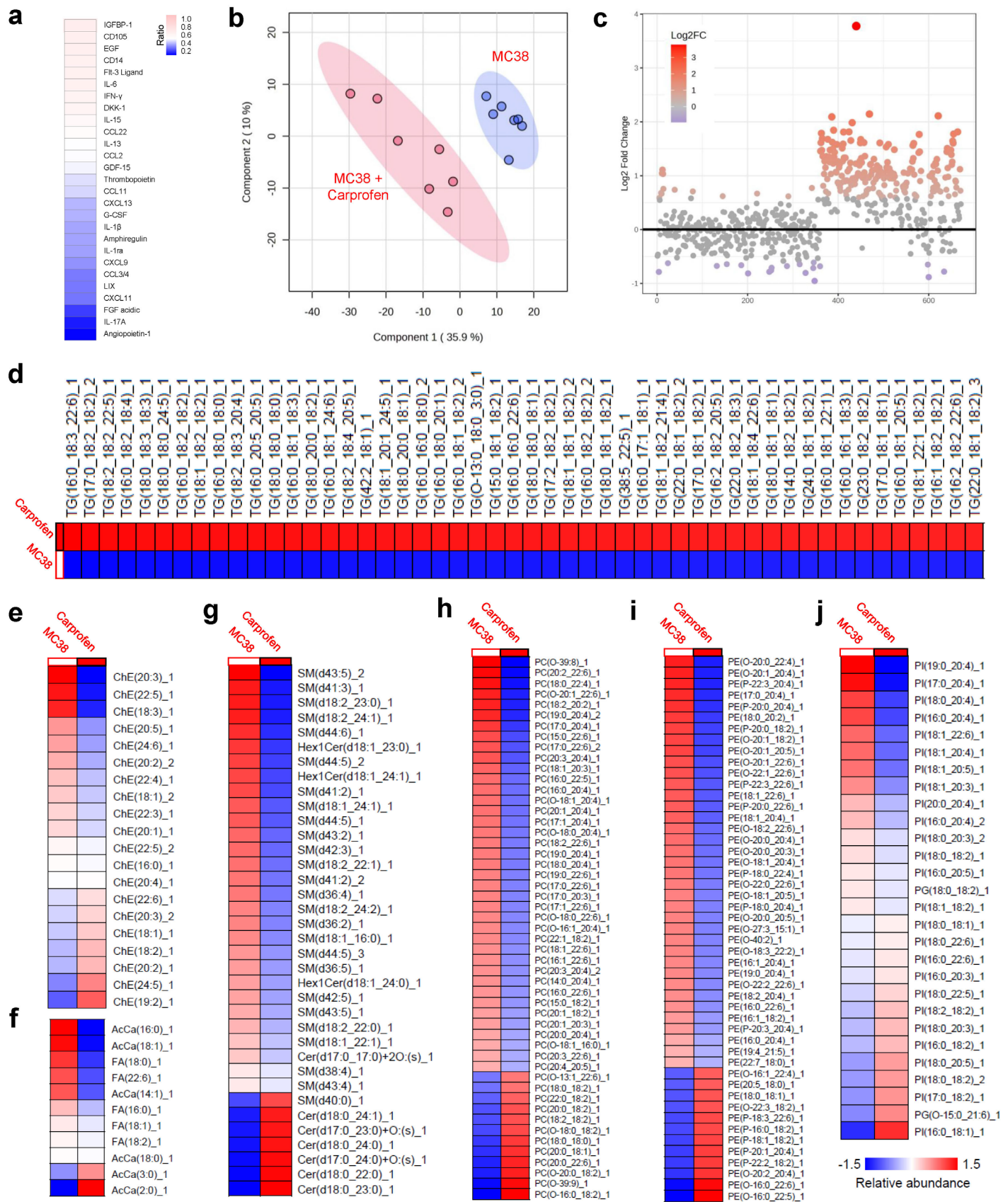
Supplementary Figure 6. Hematological measures of metabolism, hemostasis, and hepatic/renal health.

(a) Three weeks after MC38 injection, blood glucose levels do not differ from vehicle-injected controls. The tail bleed assay shows a non-significant trend toward reduced bleeding time in MC38 mice ($t(18) = 1.875$, $p = 0.077$), which is associated with a non-significant overall reduction in blood loss ($t(18) = 1.37$, $p = 0.188$), a significant elevation in fibrinogen ($t(6) = 3.671$, $p = 0.01$), and a non-significant trend toward reduced fibrinogen time ($t(6) = 1.732$, $p = 0.134$). (b) Prothrombin, antithrombin, and activated partial thromboplastin time (aPTT) do not significantly differ. (c) Liver markers alkaline phosphatase, gamma-glutamyltransferase and alanine transaminase are not significantly elevated in MC38 mice, whereas aspartate transaminase is significantly elevated ($t(6) = 2.47$, $p = 0.048$). (d) Renal function as assessed by an electrolyte panel and creatinine appear normal in MC38 mice. Dual liver/kidney function markers albumin and total protein also do not differ. (e) A non-significant trend toward upregulation of tissue damage markers lactate dehydrogenase ($t(6) = 2.395$, $p = 0.054$) and creatine kinase ($t(6) = 0.946$, $p = 0.381$) in MC38 tumor mice. Error bars = SEM. Two-sided unpaired T-test. Source data are provided as a Source Data file.



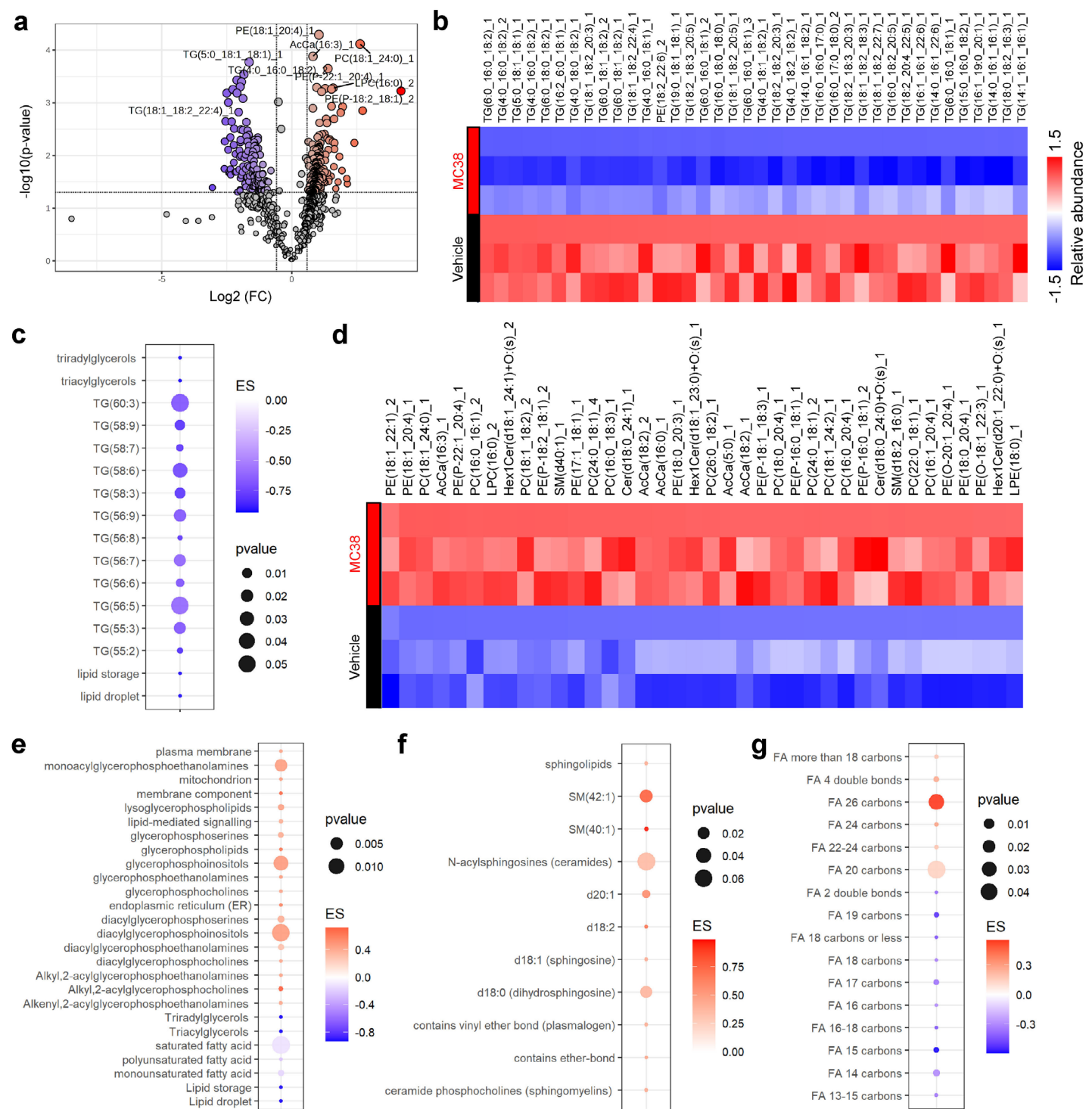
Supplementary Figure 7. Gut integrity is not overtly compromised in MC38 mice at week 3. (a) Oral dosing with a FITC-dextran conjugate was carried out three weeks after MC38 or vehicle injection. Four hours later, blood samples were collected and FITC fluorescence was measured. No significant difference was seen between vehicle and MC38-injected mice. (b) A significant main effect of MC38 tumor growth on plasma lipocalin-2 levels ($F_{1,6} = 8.997$, $p = 0.024$), with significantly elevated lipocalin-2 in MC38 mouse plasma at week 4 ($p = 0.023$). (c) No significant elevation in fecal lipocalin-2 content. (d) Luminol did not detect any significant increase in fecal hemoglobin content in MC38 mice at three weeks post-injection ($t(8) = 1.652$, $p = 0.137$), two-sided unpaired t-test. (e-h) H&E sections of colon appear grossly normal in vehicle and MC38-injected mice. Dotted lines show region magnified in adjacent panel. At higher magnifications, a modest increase in cellularity was noted in MC38 tumor-bearing mice. Magnification 10x, scale bars = 0.4 mm (e, g), 20x, 0.1 mm (f, h). Source data are provided as a Source Data file.

Heatmap and enrichment score (ES; **g**) shows widespread depletion of triglycerides in tumor-bearing mice. (**h**) Chain length analysis shows an enrichment of long-chain fatty acids and depletion of shorter-chain molecules. (**i**) Saturation index shows enrichment of several polyunsaturated fatty acids alongside depletion of saturated and monounsaturated fatty acids. (**j-k**) Analysis of lipid class enrichment reveals increased ceramides and sphingomyelins. (**l**) Cholesterol esters are enriched in plasma from tumor-bearing mice (**m**) Phosphatidylcholines (PC) are majority enriched in MC38 plasma (**n**) Phosphatidylethanolamines (PE) are majority reduced in MC38 plasma. (**o**) Lysophosphatidylcholine/ethanolamine show similar enrichment/depletion dynamics to PC/PE (**p**) Phosphatidylinositol (PI) abundance is highly variable, with some enrichment and some depletion in MC38 tumor-bearing mice. Vehicle n=3 technical replicates, MC38 n=3 technical replicates, each composed of two pooled biological replicates. Source data are provided as a Source Data file.



Supplementary Figure 9. Effect of carprofen on plasma lipids in MC38 mice. (a) Proteome profiler array of MC38 mouse serum shows expected downregulation of inflammatory mediators associated with carprofen treatment (particularly IL-1 β , IL-6, CCL2 and G-CSF). Pooled results from n=2 technical replicates, each composed of n=3 biological replicates. (b) PCA plot indicates substantial separation of plasma samples from MC38 mice with and without carprofen treatment, (c)

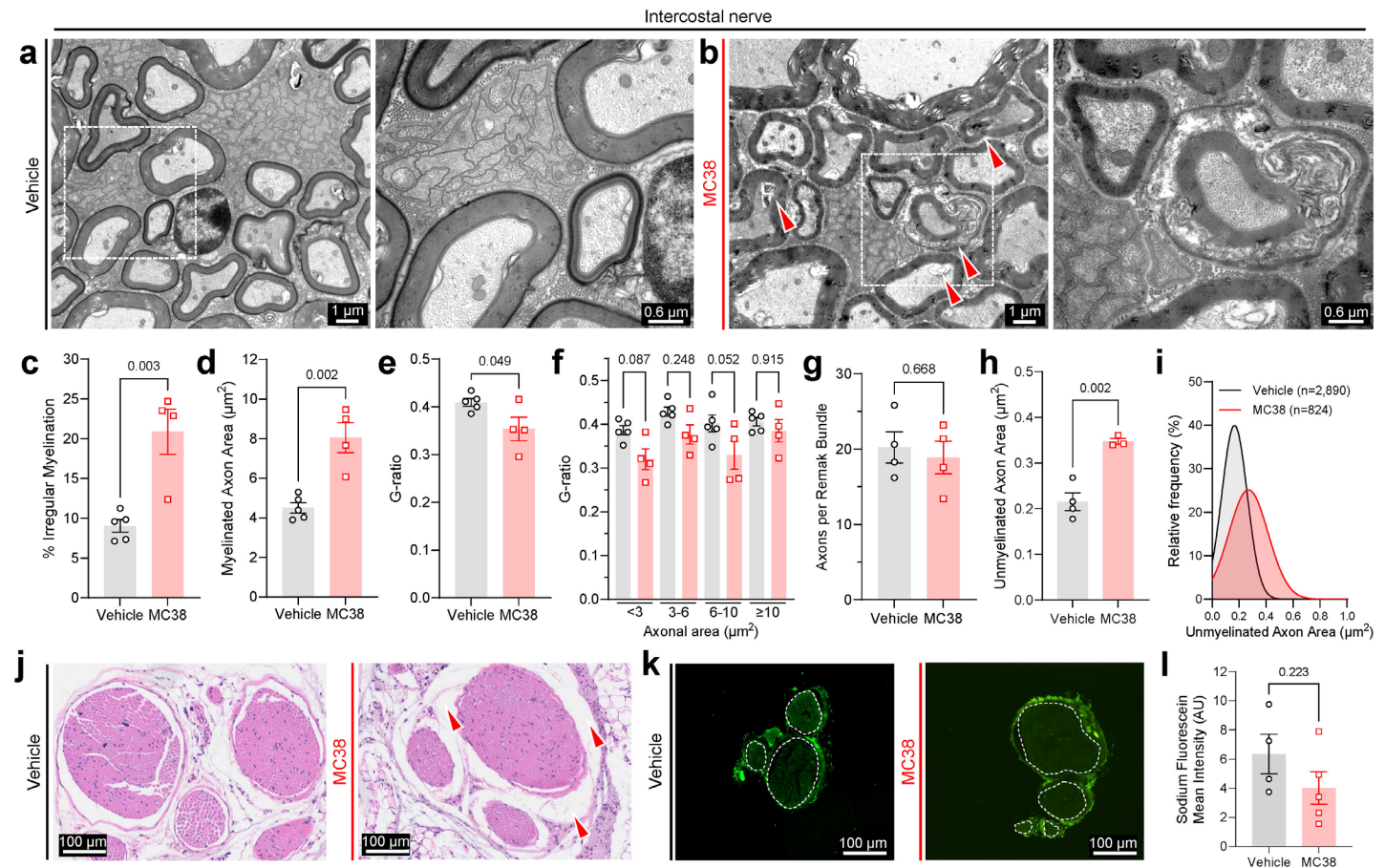
reflected in the substantial number of differentially abundant lipid species. **(d)** Elevated plasma triglycerides in carprofen-treated mice. **(e)** Carprofen is also associated with depletion and enrichment of cholesterol esters, **(f)** depletion of acylcarnitines, **(g)** depletion of sphingomyelins and enrichment of ceramides, **(h-i)** majority depletion of PC and PE species, **(j)** with no consistent directional change in PI species. Vehicle n=7 technical replicates, MC38 n=7 technical replicates, each derived from a single biological replicate. Source data are provided as a Source Data file.



Supplementary Figure 10. Lipidomic profiling of additional control and MC38 tumor-bearing mouse sciatic nerves. (a) Volcano plot displaying log2 fold-change and p-value of lipid abundance

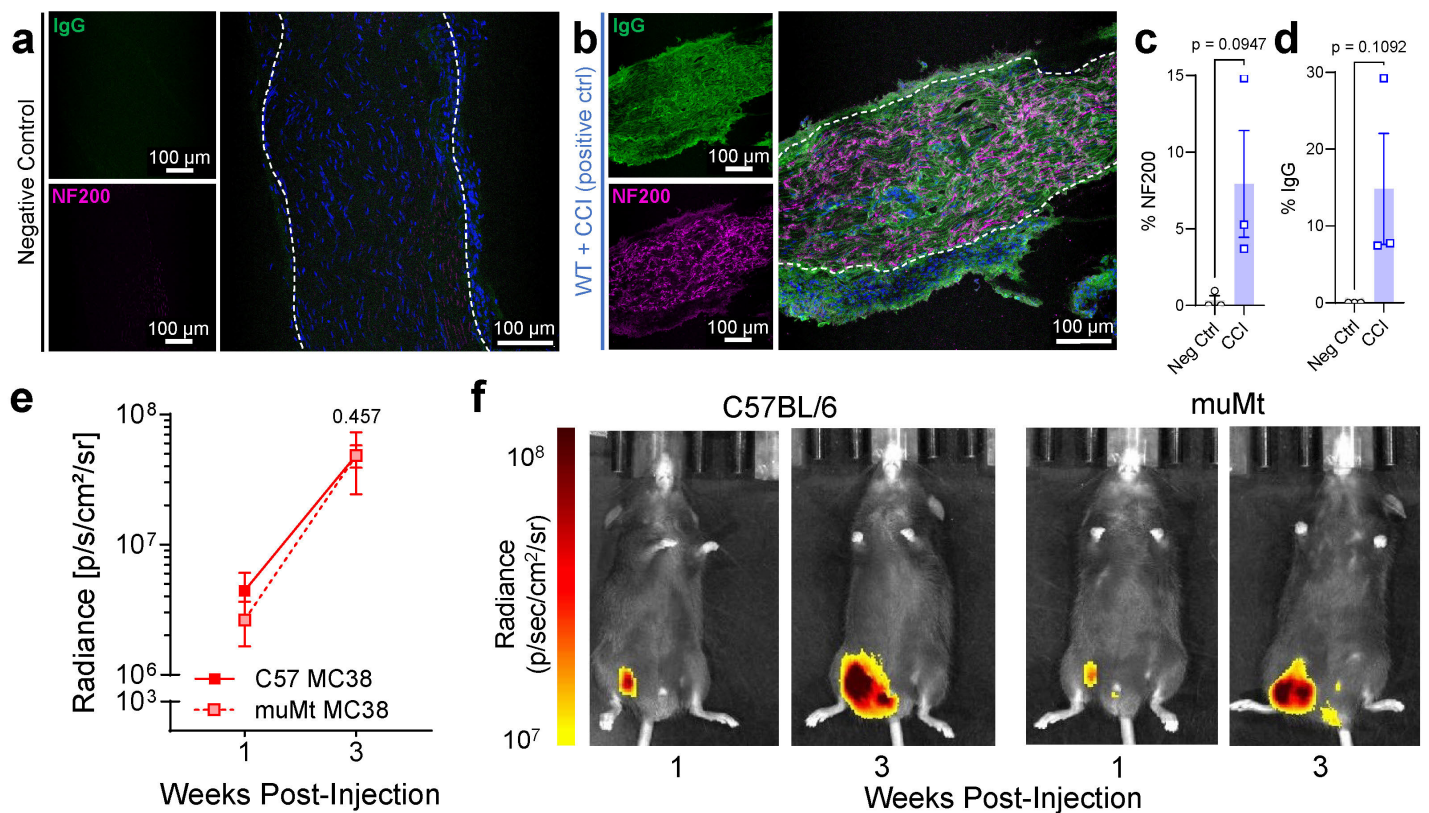
in MC38 tumor-bearing mouse sciatic nerve versus control. **(b-c)** Heatmap and enrichment scores show widespread depletion of triglycerides in tumor-bearing mice. **(d)** Phosphatidylethanolamines (PE), sphingomyelin, PC, ceramides and hexosylceramides are enriched in sciatic nerves from MC38 tumor mice. **(e)** Analysis of lipid class enrichment reveals increased diacylglycerolipids and reduced triacylglycerols. **(f)** Sphingolipids and ceramides are significantly enriched in MC38 plasma. **(g)** Chain length analysis shows enrichment of fatty acids > 18 carbons in length, and depletion of fatty acids of shorter chain lengths. Vehicle n=3 technical replicates, MC38 n=3 technical replicates, each composed of two pooled biological replicates. Source data are provided as a Source Data file.

family 25, member 18), *Slco2a1* (solute carrier organic anion transporter family member 2a1), *Pltp* (phospholipid transfer protein), *Lpl* (lipoprotein lipase), *Pitpnb* (phosphatidylinositol transfer protein beta), *Pmp22* (peripheral myelin protein 22), *Pmvk* (phosphomevalonate kinase), *Smpd2* (sphingomyelin phosphodiesterase 2), *Ebp* (emopamil binding protein), *Sdc1* syndecan 1), *Slc10a6* (solute carrier family 10, member 6), *Akr7a5* (aldo-keto reductase family 7 member A5), *Arxes2* (adipocyte-related X-chromosome expressed sequence 2), *Mag* (myelin-associated glycoprotein), *Bdnf* (brain-derived neurotrophic factor), *Arxes1* (adipocyte-related X-chromosome expressed sequence 1), *Myrf* (myelin regulatory factor) and *Ryr1* (ryanodine receptor 1). (b-d) Intercostal nerves show a significant increase in S100B immunoreactivity ($t(4) = 3.034$, $p = 0.039$). (e) Negative control for S100B immunolabeling. (f-h) Significant reduction in S100B staining density in sciatic nerves from MC38 mice treated with carprofen ($t(4) = 4.405$, $p = 0.012$). (i) Sciatic nerve shows no significant reduction in myelinated axon area ($n=7-8$ biological replicates per group). (j) G-ratio is significantly lower in nerves of all axonal areas ($n=7-8$ biological replicates per group). (k) Rightward shift in size distribution of unmyelinated axons in MC38 mouse sciatic nerve. (l) Bulk RNA-sequencing of cultured Schwann cells exposed to MC38 mouse serum shows upregulation of processes consistent with dedifferentiation and proliferation. Error bars = SEM. Two-sided unpaired T-test. Scale bars = 100 μ m. Source data are provided as a Source Data file.

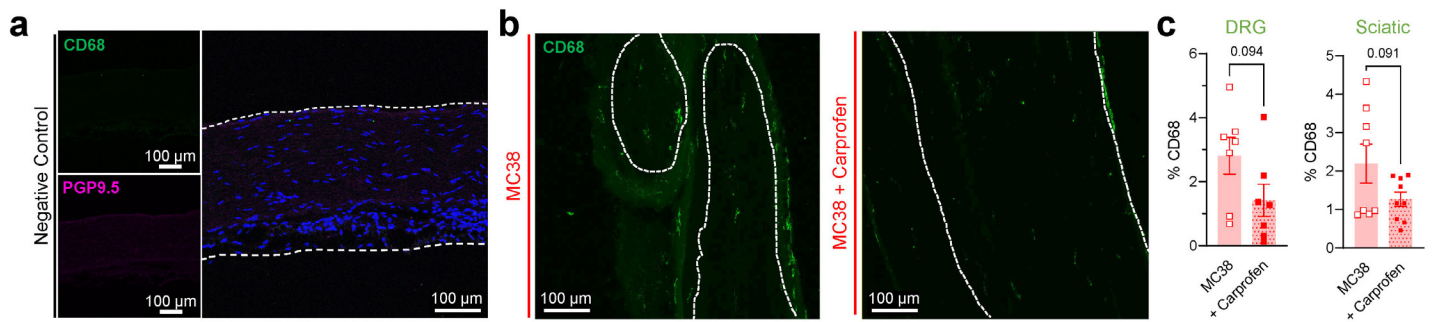


Supplementary Figure 12. Intercostal nerve TEM and sciatic nerve edema/permeability. (a-c) Significantly increased irregular myelination in intercostal nerves of MC38 mice ($t(7) = 4.45$, $p = 0.003$). Dotted line shows area magnified in adjacent panel. Scale bars = 1 μ m (main image), 0.6 μ m (inset). (d) Significantly increased area of myelinated axons ($t(7) = 4.838$, $p = 0.002$) (e) and

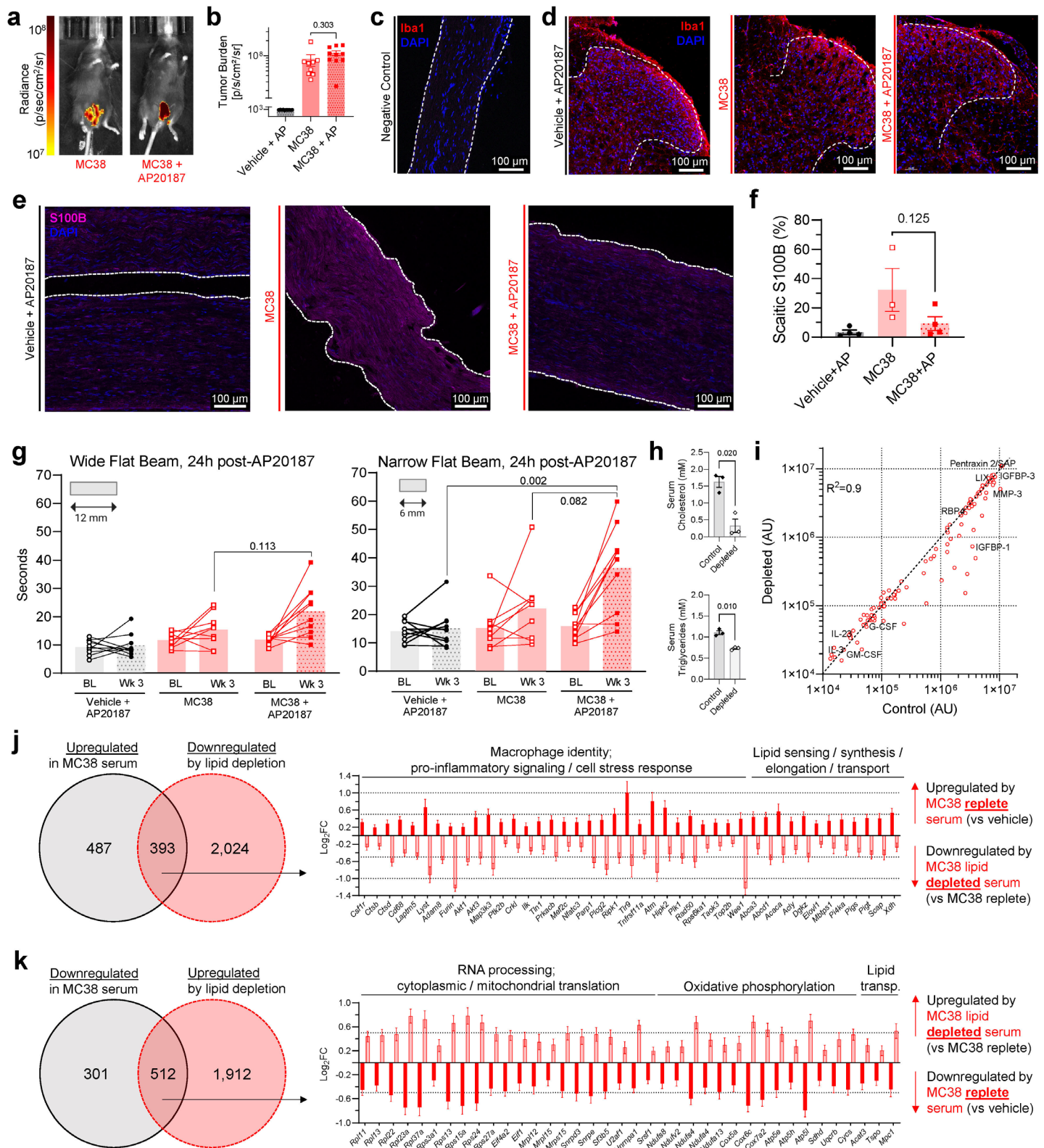
significantly reduced G-ratio ($t(7) = 2.374$, $p = 0.049$). (f) Reduced G-ratio ($F_{7, 28} = 3.613$, $p = 0.007$), shows a non-significant tendency to be present in all but the largest axons ($n=4-5$ biological replicates per group). (g) No significant change in the number of axons per Remak bundle ($t(4) = 0.713$, $p = 0.515$), (h-i) with a significant increase in unmyelinated axon cross-sectional area ($t(5) = 5.669$, $p = 0.002$). Two-sided unpaired t-test/one-way ANOVA, Šídák's multiple comparisons test, $n=3-4$ biological replicates per group. (j) Samples from MC38-injected mice show evidence of sub-perineurial edema (red arrowheads), without any obvious increase in cellular density or edema in the epineurium or endoneurium. Black boxes illustrate the area of the magnified image. Scale bars = 100 μm . (k) Representative images of sodium fluorescein extravasation into the endoneurium (dotted white lines), quantified in (l) ($t(7) = 1.336$, $p = 0.223$). Two-sided unpaired t-test. Scale bars = 100 μm . Source data are provided as a Source Data file.



Supplementary Figure 13. IgG deposition and MC38 tumor development in muMt mice. (a) Negative control images of IgG immunolabeling in wild-type mice. (b) Chronic constriction injury (CCI) of the sciatic nerve induces IgG deposition, quantified in (c-d). Scale bars = 100 μm . (e-f) No significant differences in MC38 tumor growth in muMt versus wild-type mice ($F_{5, 5} = 1.107$, $p = 0.457$, two-sided two-way ANOVA, Šídák's multiple comparisons test). Error bars = SEM. Scale bars = 100 μm . Source data are provided as a Source Data file.

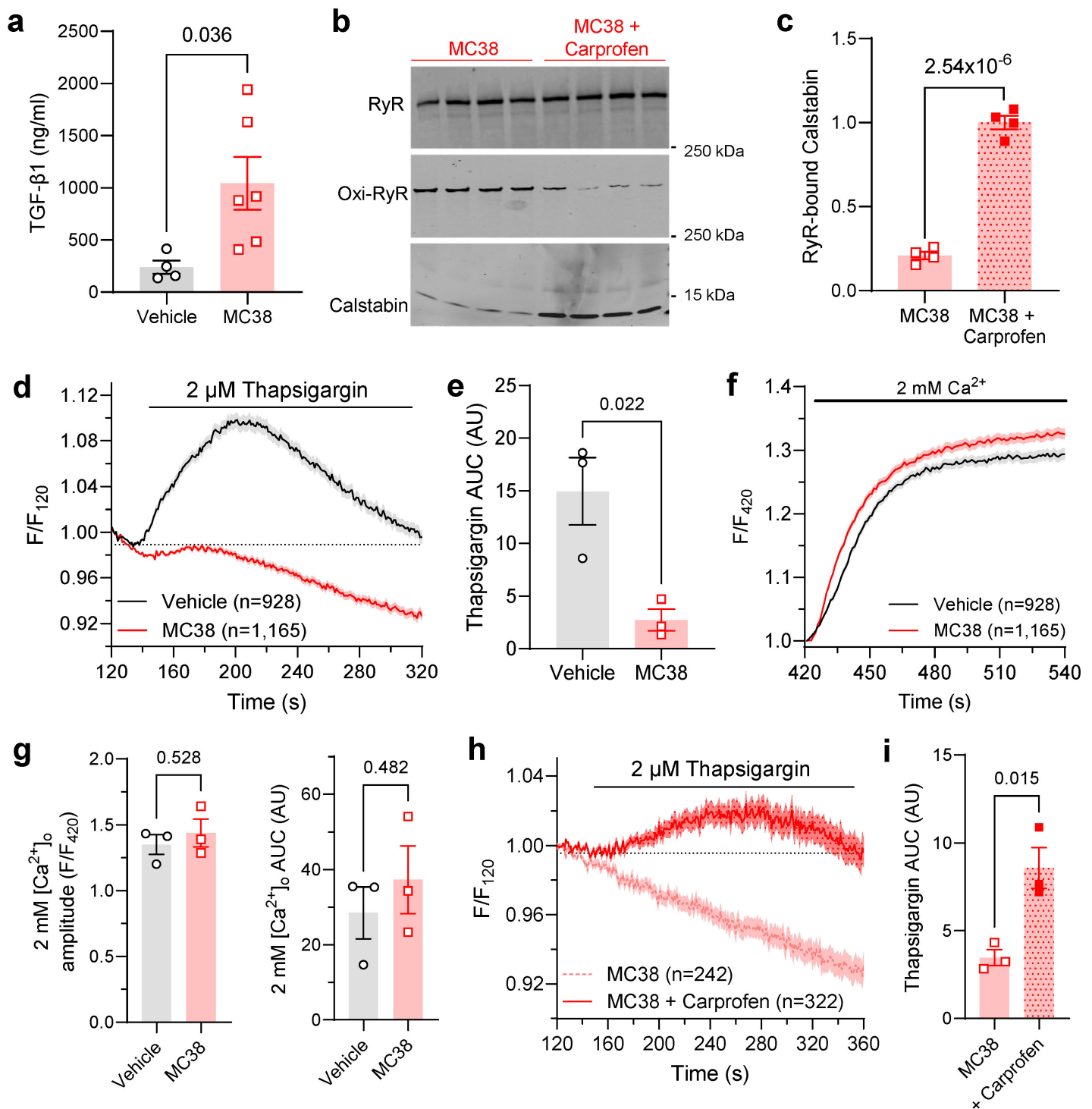


Supplementary Figure 14. Sciatic nerve macrophage immunostaining of carprofen-treated MC38 mice. (a) Negative control image for CD68 (green) / PGP9.5 (magenta) immunostaining in sciatic nerve. Scale bar = 50 μ m. (b-c) Carprofen treatment of MC38 mice is associated with a non-significant decrease in CD68 staining density in DRG ($t(15) = 1.807$, $p = 0.091$) and sciatic nerve ($t(12) = 1.82$, $p = 0.094$). Error bars = SEM, two-sided unpaired T-test. Error bars = SEM. Scale bars = 100 μ m. Source data are provided as a Source Data file.

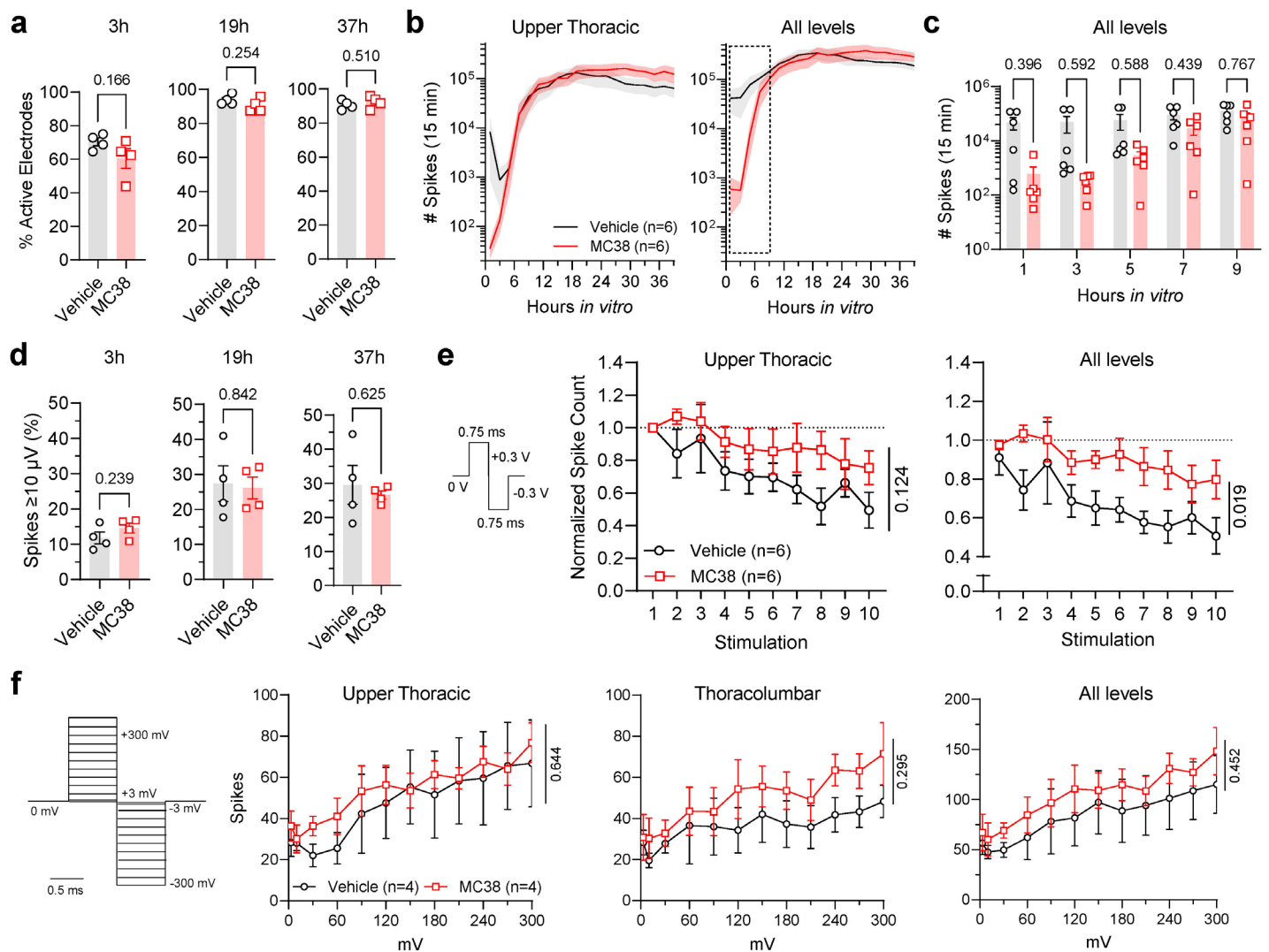


Supplementary Figure 15. MaFIA mouse immunostaining and behavioral testing. (a-b) No significant effect of AP20187 on MC38 tumor burden in MaFIA mice ($F_{2,26} = 2.135$, $p = 0.303$). **(c)** Negative control of Iba1 immunostaining in mouse sciatic nerve (DAPI = blue). **(d)** Spinal cord dorsal horn shows no obvious effects of AP20187 treatment on Iba1⁺ microglial morphology/density. **(e-f)** Sciatic nerve S100B is unaffected by AP20187 treatment in vehicle control mice; MC38 mice show elevated S100B immunoreactivity which shows a non-significant trend toward reduction in MC38 mice treated with AP20187 ($t(8) = 2.14$, $p = 0.125$, one-way ANOVA, Šidák's multiple comparisons test).

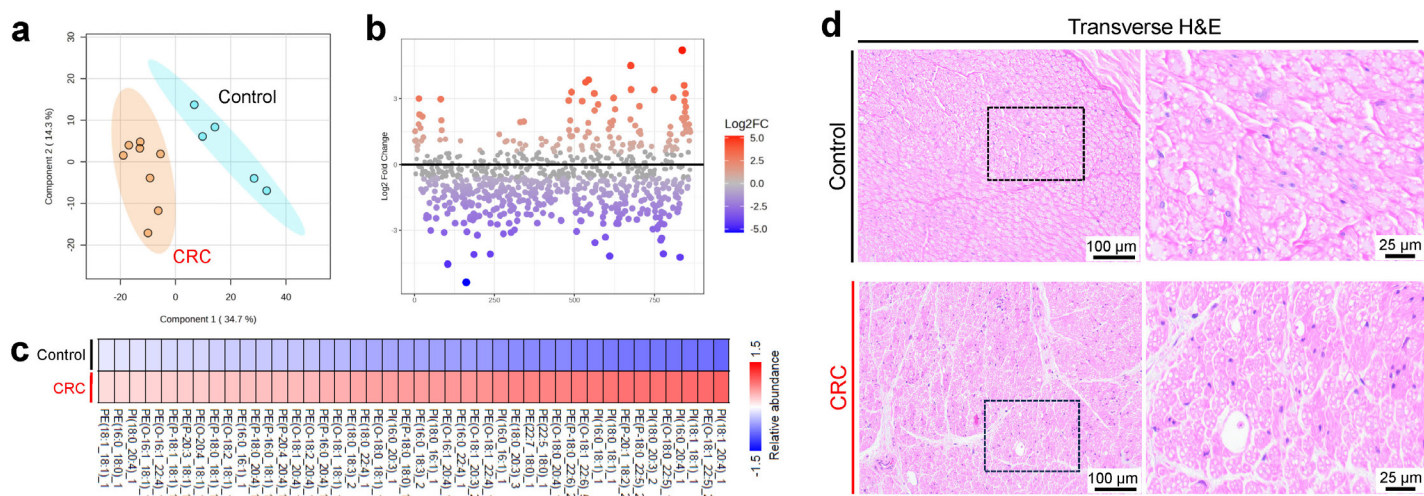
(g) AP20187 treatment in MC38 mice is associated with a trend to worsening performance on the wide flat beam ($t(27) = 1.978$, $p = 0.113$) and narrow flat beam ($t(26) = 2.141$, $p = 0.082$; aligned rank transformed one-way ANOVA, Šidák's multiple comparisons test). (h) Lipid depletion significantly reduces serum cholesterol ($t(2) = 6.994$, $p = 0.02$) and triglyceride content ($t(2) = 9.846$, $p = 0.01$). Paired T-test. (i) Lipid depletion has little to no effect on serum cytokine content. Proteome profiler array-based correlation of serum cytokine abundance in depleted versus lipid-intact healthy control mouse serum samples. Labeled factors are those previously detected at elevated levels in MC38 mice¹. (j) (left) Of the 880 genes whose expression in BMDMs was upregulated by exposure to MC38 mouse serum (versus vehicle control mouse serum), 393 were also downregulated when exposed to lipid-depleted MC38 serum. Representative genes and log₂ fold-change in transcript abundance are reproduced in the bar graph (right). (k) (left) Conversely, of the 813 genes downregulated by exposure to MC38 mouse serum, 512 were also upregulated when exposed to lipid-depleted MC38 serum. Representative genes and log₂ fold-change in transcript abundance are reproduced in the bar graph (right). Values are based on three technical replicates (BMDM cultures), each generated using two pooled biological replicates (sera). Scale bars = 100µm. Error bars = SEM. Source data are provided as a Source Data file.



Supplementary Figure 16. Carprofen effect on RyR oxidation and thoracic DRG Ca^{2+} imaging. (a) TGF- β is significantly elevated in MC38 mouse serum ($t(8) = 2.522$, $p = 0.036$). (b-c) Carprofen treatment significantly reduces RyR oxidation ($t(6) = 17.12$, $p = <0.0001$). (d-e) Upper thoracic level DRG neurons from MC38 mice show similar lack of thapsigargin responsiveness to lumbar level neurons, along with significantly reduced AUC ($t(4) = 3.647$, $p = 0.022$; two-sided unpaired t-test). (f-g) No significant change in Ca^{2+} influx rate ($t(4) = 0.6902$, $p = 0.528$) or amplitude ($t(4) = 0.774$, $p = 0.482$) in thoracic DRG from MC38 mice. (h-i) Carprofen treatment of MC38 mice is associated with restored thapsigargin responsiveness of DRG neurons and significantly increased AUC ($t(4) = 4.11$, $p = 0.015$). Two-sided unpaired t-test. Error bars = SEM. Unpaired T-test. Source data are provided as a Source Data file.



Supplementary Figure 17. Spontaneous and electrically-evoked activity in sensory neurons from control and MC38 tumor mice. (a) No significant differences between MC38 and control mouse DRG neurons in the proportion of electrodes with spontaneous activity across time. (b) spike counts from upper thoracic DRG only (left panel) and all levels combined (b right panel, c) show a non-significant trend toward reduced activity in MC38 DRG in the first ~9 hours *ex vivo*, with a significant main effect of time ($F_{1,187, 11.87} = 11.11$, $p = 0.005$) two-sided two-way repeated measures ANOVA, Šidák's multiple comparisons test. (d) Thoracic MC38 DRG do not show a significant reduction in spike amplitude across time ($n=4$ biological replicates per group). (e) Thoracic DRG show a non-significant trend toward impaired desensitization with repeated electrical stimulation ($F_{1, 10} = 2.818$, $p = 0.124$), which becomes a significant main effect when thoracic and lumbar datasets are combined ($F_{1, 10} = 7.815$, $p = 0.019$). (f) Ramp stimulation of thoracic and lumbar DRG show a modest, non-significant tendency toward increased activity in MC38 neurons across all levels ($n=4$ biological replicates per group, each composed of activity readings from $n \leq 48$ electrodes distributed across $n=3$ wells). Two-sided, two-way repeat measures ANOVA, Šidák's multiple comparisons test. Source data are provided as a Source Data file.



Supplementary Figure 18. Rhesus macaque plasma lipidomics and sciatic nerve histology. (a) PCA plot indicates substantial separation of plasma samples from rhesus macaques with and without a CRC diagnosis. (b) This separation is reflected in the substantial number of differentially abundant lipid species. (c) Elevated plasma PE and PI species in CRC macaques. (d) Transverse sections of sciatic nerve from CRC macaques show more signs of edema and degeneration. Dotted line shows area magnified in adjacent panel. Scale bars = 100µm (main image), 25µm (inset). Source data are provided as a Source Data file.

Supplementary Video Files 1-3: Male vehicle vs MC38 tumor, week 3, wide flat, narrow flat, round beams.

Supplementary Video Files 4-6: Female vehicle vs MC38 tumor, week 3, wide flat, narrow flat, round beams.

References:

- 1 Balogh, M. *et al.* Sensory neuron dysfunction in orthotopic mouse models of colon cancer. *Journal of neuroinflammation* **19**, 204 (2022). <https://doi.org/10.1186/s12974-022-02566-z>