Inflammatory Neuropathy in Mouse and Primate Models of Colorectal Cancer

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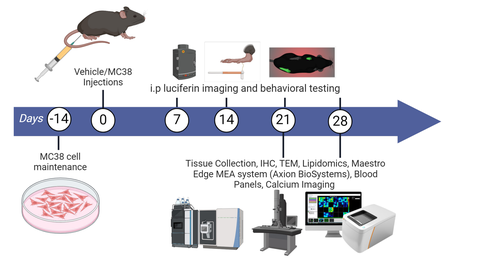
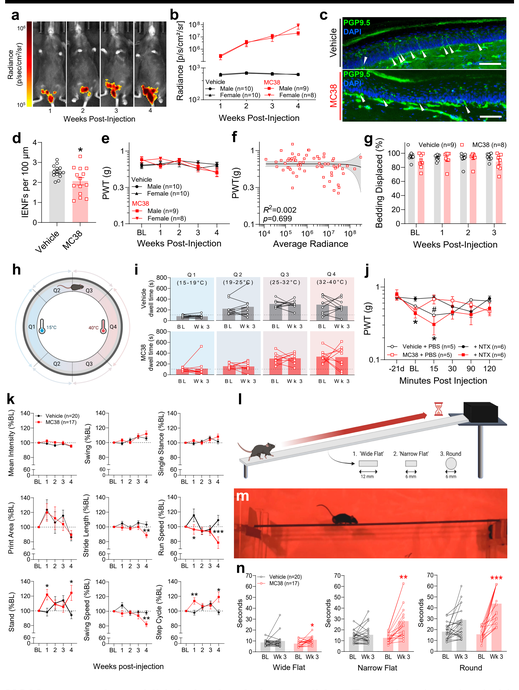
Abstract

Colorectal cancer (CRC) survivors are at increased risk of developing neurological issues, particularly peripheral neuropathy and chronic pain. Although pre-existing neuropathy is a risk factor for chronic pain, tumor-induced neuropathy has not been firmly established in pre-clinical models. Consistent with clinical observations, mice with CRC develop peripheral neuropathy, which is associated with subtle locomotor deficits, without overt hypersensitivity. Peripheral nerves from CRC mice show widespread differences in pro-inflammatory cytokines and lipid metabolites, along with macrophage accumulation and myelin decompaction. In DRG neurons, ryanodine receptor oxidation was associated with dysfunctional Ca^{2+} homeostasis and reduced spike amplitude. Similar inflammatory neuropathy and macrophage accumulation was observed in peripheral nerves of rhesus macaques with CRC. These findings suggest CRC can be causally linked to a subacute form of chronic inflammatory demyelinating polyneuropathy across species, which may represent an under-reported, yet important risk factor for neurological dysfunction in CRC survivors.

Materials & Methods

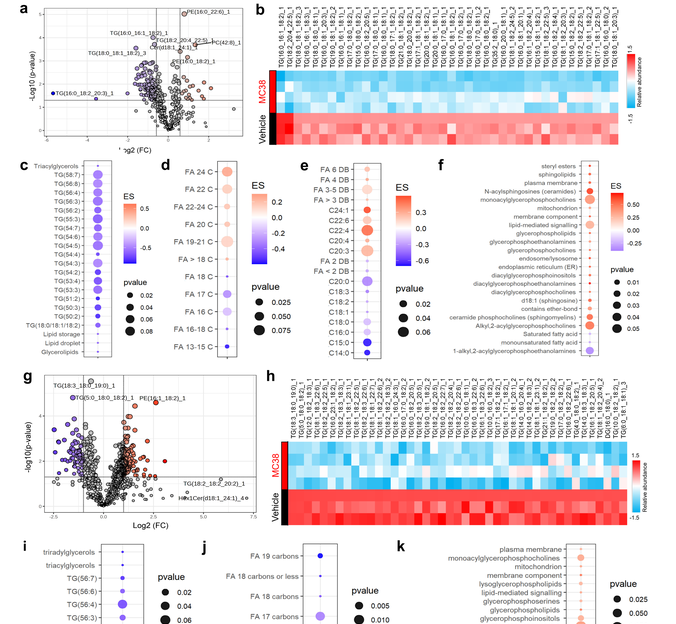


Behavioral Analysis



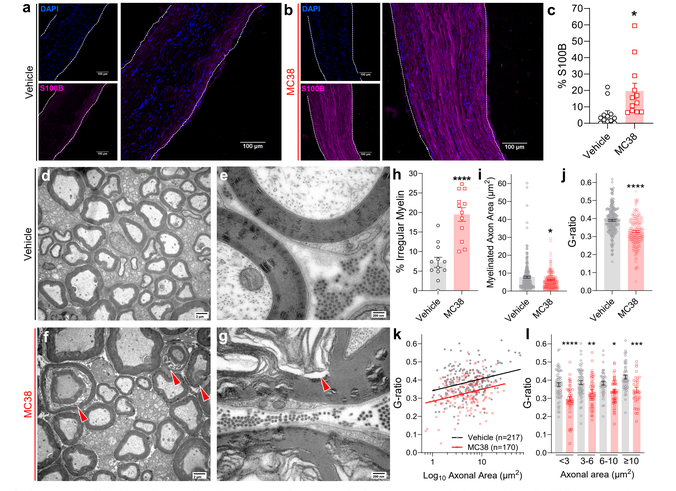
MC38 tumor mice exhibit behavioral abnormalities. Tumor bearing mice (**a-b**) show IENF loss (**c-d**), but unaltered tactile/thermal sensitivity (**e-j**). Minor gait abnormalities (**k**) and deficits in motor coordination (l-n) were observed.

Plasma & Sciatic Nerve Lipid Dysregulation



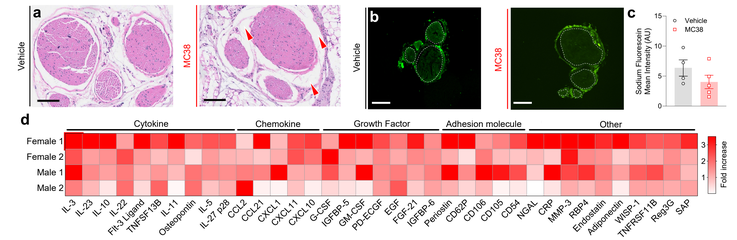
MC38 CRC dysregulates plasma and sciatic nerve lipids. MC38 tumor-bearing mouse plasma (**a-f**) and sciatic nerve (**g-k**) show similar upregulation of inflammatory lipid species associated with neuropathy alongside widespread and marked downregulation of triglycerides.

Schwann Cell Injury & Demyelination



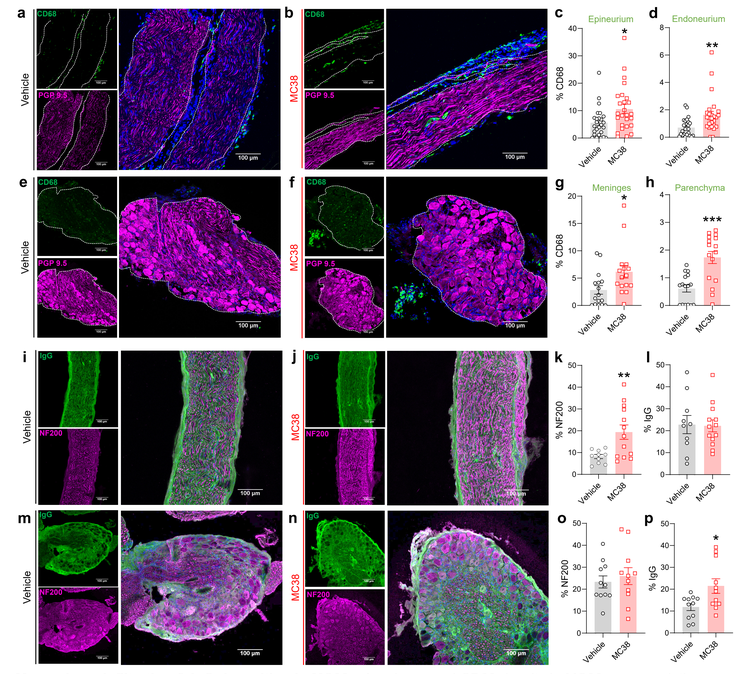
Schwann cell injury & myelin decompaction in sciatic nerves of MC38 mice. S100B expression was significantly elevated in sciatic nerves from tumor-bearing mice (**a-c**). Transverse TEM images of sciatic nerves from MC38 tumor-bearing mice show numerous irregularities in myelination (**d-l**).

Peripheral Nerve Inflammation & Integrity



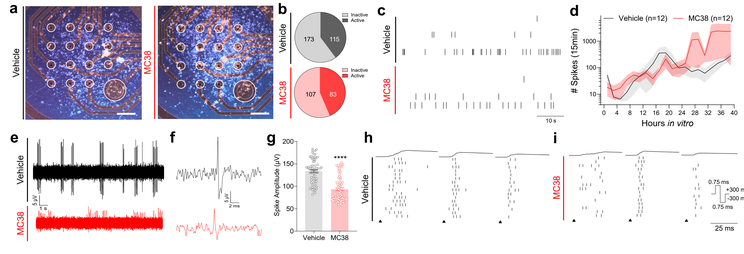
MC38 tumor growth is associated with peripheral nerve inflammation. MC38 mice exhibit evidence of epineural edema, but do not show loss of blood-nerve barrier integrity (**a-c**). MC38 mouse sciatic nerves showed upregulation of numerous inflammatory mediators, including cytokines, chemokines, growth factors, and adhesion molecules (**d**).

Macrophage Infiltration and IgG Deposition



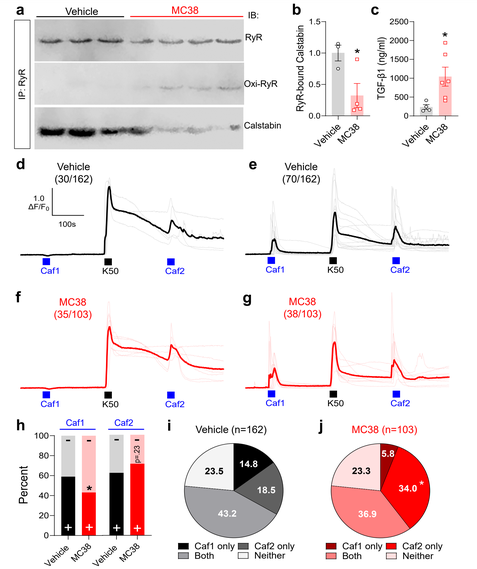
Macrophage infiltration & IgG deposition in MC38 mice. Increased CD68 density in MC38 mouse sciatic nerves (**a-d**) and DRG (**e-h**), increased NF200 density in the sciatic nerve (**i-l**) and elevated IgG content in the DRG (**m-p**).

Spontaneous and Evoked Activity in DRG Neurons



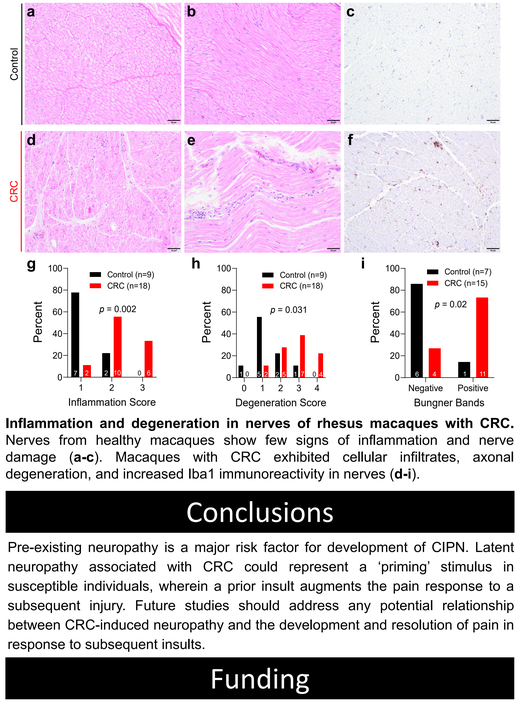
DRG neuron spontaneous activity was not adversely affected by MC38 tumor growth (a-d). Spike amplitudes reduced in MC38 mouse DRG neurons (**e-g**), and electrically-evoked action potentials were not affected (**h-i**).

Ca^{2+} Homeostasis in DRGs



TGFβ and RyR oxidation are associated with DRG neuron dysfunction in MC38 tumor-bearing mice. TGF-β-driven oxidization of neuronal RyR (**a-c**) causes Ca^{2+} leak and depletes ER Ca^{2+} stores in DRG neurons (**d-j**).

CRC in Rhesus Macaques



Inflammation and degeneration in nerves of rhesus macaques with CRC. Nerves from healthy macaques show few signs of inflammation and nerve damage (**a-c**). Macaques with CRC exhibited cellular infiltrates, axonal degeneration, and increased Iba1 immunoreactivity in nerves (**d-i**).

Conclusions

Pre-existing neuropathy is a major risk factor for development of CIPN. Latent neuropathy associated with CRC could represent a 'priming' stimulus in susceptible individuals, wherein a prior insult augments the pain response to a subsequent injury. Future studies should address any potential relationship between CRC-induced neuropathy and the development and resolution of pain in response to subsequent insults.

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