**Figure S1. Immunohistochemical and morphological analyses of healthy and tumor bearing colons. a-f,** Confocal images of a colon from *ApcWT*+control rat (**a, b**) and colon and colon tumors from *ApcPirc/+*+control (**c, d**) and *ApcPirc/+*+OX rats (**e, f**). Immunolabeling shows expression of DAPI and Ki-67, and EGFR a measure proliferative growth associated with tumor progression. White dotted boxes in wide-field images (**a, c, e**) outline region of interest (**b, d, f**). White arrows indicate smooth muscle boundary used as anatomical reference.

**Figure S2. Longitudinal change in animal weight.** Longitudinal study of animal weights reveals systemic non-linear interaction of cancer and chemotherapy. Weekly weight measures tracking systemic effects of cancer and/or chemotherapy. Rats included were used for transcriptional, protein, and physiologic studies. Data are mean ± s.d. from 15 *ApcWT*+control, 10 *ApcWT*+OX, 6 *ApcPirc/+*+control, and 8 *ApcPirc/+*+OX rats.

**Figure S3. List of Parameters used for Neurophysiological Analyses.** **a,** Measured and derived parameters were computed offline using custom written MATLAB scripts. Letters in the left column indicate the specific parameters included in analyses for each functional feature cluster. Thr: threshold (9 parameters); Dyn: dynamic (11 parameters); Stat: static (8 parameters); HxDep: history-dependent (1 parameter). **b**, Representative fast ramp-hold-release (3 mm at 20mm/s) trial from a proprioceptive neuron recorded from dorsal roots in *in vivo* electrophysiological experiments of a wild-type rat. **c**, Representative slow repeated ramp (3 mm at 4mm/s) trial from a proprioceptive neuron recorded from dorsal roots in *in vivo* electrophysiological experiments of a wild-type rat. Corresponding action potential trains and overlaid black circles indicate individual action potentials (spikes) and instantaneous firing rates (IFRs) of the responses. Dashed line marks the point of muscle stretch from background length (Lo) and indicates the starting point for threshold/sensitivity measurements. Boxes indicate dynamic (dark grey, 150 ms duration after stretch command onset) and static phases for analysis (light grey, 1 s duration after the dynamic phase)

**Figure S4. ‘Kruschke style’ hierarchical model graphical diagram.** Robust Bayesian linear regression was used to model the data yi as a t-distributed random value around the central tendency μi = β0 + β1xi . The intercept β0 and slope β1 were given broad normal priors that are vague to the scale of data. σ was given an uninformative uniform prior, and the normality parameter ν was given a broad exponential prior.

**Figure S5. Exemplar Graphical Bayesian Model Validation. a,** Time series trace plot of the Markov chains (n=4) shows the evolution of parameter (n=5) vectors over the all iterations and indicate chains explored the full parameter space. **b,** Autocorrelation of parameters (columns) illustrate the degree of correlation between MCMC samples separated by different lags (x-axis). For example, a lag of 0 represents the degree of correlation between each MCMC sample and itself (correlation of 1). A lag of 1 represents the degree of correlation between each Markov chain Monte Carlo (MCMC) sample and the next sample along the chains (rows). Independent (uncorrelated) samples (autocorrelation of 0) indicate unbiased estimates of parameters. No parameters violate autocorrelation. **c,** Shows overlaid histograms of the (centered) marginal energy distribution *πE* and the first-differenced distribution *πΔE*. The MCMC No-U-Turn Sampler (NUTS) Energy diagnostic identifies overly heavy tails that are also challenging for sampling and quantifies the heaviness of the tails of the posterior distribution. The two distributions are well-matched, meaning the random walk will explore the marginal energy distribution extremely efficiently. **d,** Plot shows one line per iteration connecting parameter values at iterations and identifies global patterns to detect divergences if present (divergences will be colored in the plot (by default in red). No divergent transitions were detected. **e,** NUTS divergence plot in the top panel shows the distribution of the log-posterior and indicates no divergences for all chains. This provides evidential support that chains adequately explore all parts of the posterior. The bottom panel shows the distribution of NUTS acceptance statistic approaches 1.

**Figure S6. Steps outlining parallel independent transcriptome analyses**. Data analysis flowchart depicts the multi-step (split into **a**, **b**, and **c** streams) approach utilized for transcriptome analysis, inferences and downstream protein level validation.Each box highlights specific analytic techniques, statistical packages (when relevant), and corresponding figures as reference. Principal component analysis, PCA; gene set enrichment analysis, GSEA; principal components, PC; Database for Annotation, Visualization and Integrated Discovery, DAVID; immunohistochemistry, IHC.

**Figure S7. Pathway analysis and GSEA based comparison of the independent effects of cancer and chemotherapy show convergence of mitochondrial dysfunction.** List of enriched gene sets in sensory neurons identified by GSEA (queried against MSigDB, C2-CP: canonical pathways; C3- MIR: microRNA targets; C3- TFT: transcription factor targets; C5-BP: GO biological process; C5- CC: GO cellular component; C5- MF: GO molecular function C7: immunologic signatures gene sets from the comparison of **a,** *ApcWT*+control and *ApcWT*+OX and **b,** *ApcWT*+control and *ApcPirc/+*+control groups. Individual frames identify functionally related groups of gene sets expressing distinct up- or downregulation as compared with control. Representative enrichment plots are shown on the right. Heat-map representation of leading-edge genes are shown on the right of each enrichment plot highlight key mitochondrion-related proc, such as translation and biogenesis in both *ApcWT*+OX and *ApcPirc/+*+control neurons, and key neuron myelinatio-related processes. Statistical significance was determined by permutation testing with normalized enrichment score (NES) and Benjamini–Hochberg false discovery rate (FDR) < 0.25.

**Figure S8. Relationship between DEG and biologic processes.** Chord diagram shows enriched pathways (Database for Annotation, Visualization, and Integrated Discovery; DAVID) on the right, and genes contributing to enrichment are shown on the left. Squares on left indicate genes differentially expressed in *ApcWT*+OX, *ApcPirc/+*+control, or *ApcPirc/+*+OX groups compared to control (see the key for gene differential expression). Statistical significance determined by permutation testing with normalized enrichment score (NES) and Benjamini–Hochberg false discovery rate (FDR) < 0.25. DEG, differentially expressed genes; ROS, reactive oxygen species: ECM, extracellular matrix.

**Figure S9. Immunostaining of sensory neurons in dorsal root ganglia**. Whole-mount staining and confocal axial projections of DRG neurons highlight expression of IL6 (a) in *ApcWT*+control, *ApcWT*+OX, *ApcPirc/+*+control, and *ApcPirc/+*+OX rats

**Figure S10. Model of molecular determinants of neuronal signaling of sensory neurons.** Model of mechanically-, voltage- and ligand-gated ion channels and their distribution in muscle spindle Ia primary ending. The intrafusal muscle fiber (red) is wrapped by an annulospiral ending (green) and a preterminal axon that extends unmyelinated from the terminal to the heminode (pink) followed by a myelinated axon. Dotted-boxes represent specific regional distributions believed to underlie specific functional characteristics of neuronal signaling e.g. mechanotransduction, receptor potential amplification, spike encoding, and autogenic feedback. Red circles with slashes indicate no gene and protein level evidential support for involvement in mediating cancer-chemotherapy codependent neuronal dysfunction. Bold question marks (**?**) indicate protein as a possible candidate due to evidential support from transcriptome, yet protein level confirmation is unavailable. **a,** Deformation of the receptor ending opens mechanotransduction channels that initiate excitatory currents mediated by ASIC2/3 (Simon et al 2010), Piezo2 (Woo et al 2015), ENaCa,b,d,g and to some extend TRP channels (Bewick and Banks 2015). Various Nav (Carrasco et al 2017) and Cav (Bewick and Banks 2015) channels are believed to amplify receptor potentials (**b**) and assist transmission toward encoding in the preterminal axons (**c**). **d**, Recent discovery of specific distribution of Nav channels in the heminodes (Carrasco et al 2017) are believed to underlie encoding of action potential similar to axon initial segments in other systems (Foust et al 2010). **e**, three components known to regulate auto- genic glutamatergic synapses in proprioceptors critical for signaling.

**Figure S11. vGlut1 immunostaining of proprioceptive sensory neurons receptor endings**. Whole-mount staining and confocal axial projection of the preterminal axons and annulospiral receptor endings of proprioceptive sensory neurons showing single channel images of vGlut1 (green) from: **a**, *ApcWT*+control rat; **b**, *ApcPirc*/++control; **c**, *ApcWT*+OX; **d**, and *ApcPirc*/++OX rats.

**Figure S12. Nav1.6 immunostaining of proprioceptive sensory neurons receptor endings**. Whole-mount staining and confocal axial projection of the preterminal axons and annulospiral receptor endings of proprioceptive sensory neurons showing single channel images of Nav1.6 (red) and NF-H (green) in top row from: **a**, *ApcWT*+control rat; **b**, *ApcWT*+OX; **c**, and *ApcPirc*/++OX rats. Bottom rows show Nav1.6 distribution in heminodes where spike encoding is initiated.

**Figure S13. ASIC2 immunostaining of proprioceptive sensory neurons receptor endings**. Whole-mount staining and confocal axial projection of the preterminal axons and annulospiral receptor endings of proprioceptive sensory neurons showing single channel images of Asic2 (red) from: **a**, *ApcWT*+control rat; **b**, *ApcWT*+OX; **c**, and *ApcPirc*/++OX rats.

**Figure S14. Heat-map distribution of significantly differentially expressed genes specific to neuron neuronal excitability.** Major voltage-gated, mechanically gated, transient receptor potential (TRP) channels and ligand-gated and G-protein coupled receptors across experimental groups. Expression patterns of different sub-types channels and receptors were identified by empirical Bayesian moderated linear fixed effects models (columns are individual samples, heat-maps). (**a**) Sodium channel levels, (**b**) calcium channel levels, (**c**) chloride channel levels (**d**) potassium channel levels, (**e**) G-protein coupled receptors (GPCRs) levels, (**f**) ligand-gated channel levels, and (**g**) TRP channel levels are plotted as heat-maps. Data row standardized (mean centered and s.d. normalized) to specific genes.

**Figure S15. Kv3.3 immunostaining of proprioceptive sensory neurons receptor endings and cell bodies. a-d,** Whole-mount staining and confocal axial projection of the preterminal axons and annulospiral receptor endings of proprioceptive sensory neurons showing merged and single channel images of Kv3.3 (red) and NF-H (green) in top row from: **a,** *ApcWT*+control rat; **b**, *ApcPirc*/++control; **c,** *ApcWT*+OX; **d**, and *ApcPirc/+*+OX rats. Individual optical planes (from z-stack projection) of axial projection highlight fine three-dimensional structural distribution of merged and single channel images of Kv3.3 (bottom). Whole-mount staining and confocal axial projections of DRG neurons highlight expression of Kv3.3 in **e,** *ApcWT*+control rat; **f**, *ApcPirc*/++control; **g,** *ApcWT*+OX; **h**, and *ApcPirc/+*+OX rats.

**Figure S16. Kv3.3 Immunostaining of neuromuscular junction.** Whole-mount staining and confocal axial projection of the neuromuscular junction showing merged images of Kv3.3 (red) and NF-H (green) from: **a,** *ApcWT*+control and **b**, *ApcPirc/+*+OX rats.

**Figure S17. Steps of In Vivo Electrophysiology Analysis**. Data analysis flowchart depicts the multi-step approach applied for single neuron physiological analyses, inferences and downstream model validation. Linear discriminant analysis, LDA.

**Figure S18. Neuronal signaling responses to slow and fast naturalistic stimulus in *ApcWT*+control and *ApcPirc/+*+OX neurons. a,** Representative fast ramp-hold-release (left, 3 mm at 20mm/s) and slow repeated ramp (right, 3 mm at 4mm/s) trial from a proprioceptive neuron recorded from dorsal roots in *in vivo* electrophysiological experiments of an *ApcWT*+control (grey) and *ApcPirc/+*+OX rat (purple). Corresponding action potential trains and overlaid black circles indicate individual action potentials (spikes) and IFRs (instantaneous firing rates) of the responses. Dashed line marks the point of muscle stretch from background length (L0) and indicates the starting point for threshold/sensitivity measurements. Boxes indicate dynamic (dark grey, 150 ms duration after stretch command onset) and static phases for analysis (light grey, 1 s duration after the dynamic phase).

**Figure S19. LD1 analysis of all neuronal parameters.** **a,** Confusion matrix illustrates the results of 10-fold cross validation of LDA model performance (repeated holdout method) that achieved overall 94.7% classification accuracy (posterior prediction check). Table values represent the sum of out-of-sample cross validation predictions (row) against true class assignment (column) **b,** Histogram plot, mean values of LD1 scores (Fig. 6) for each group were compared with hierarchical Bayesian ANOVA model. Asterisk indicate statistically significant differences between experimental groups in hierarchical Bayesian ANOVA, (\*) indicates 95% highest density intervals (HDI) do not overlap between groupwise contrasts. **c,** Vectors represent the magnitude and direction of the independent and combinatorial effects of cancer and/or chemotherapy. **d,** Parameters (n =31, middle) and respective discriminant coefficients weights with the interaction-specific LD1, were regrouped into functional feature clusters (left). Histogram plots report mean values for individual parameters (right, a-k) with significant contribution to LD1 loading. Symbol (Δ) indicate parameters are included in Fig. 5 and 6. Analyzed from *ApcWT*+control (n = 11), *ApcWT*+OX (n = 19), *ApcPirc/+*+control (n = 20) and *ApcPirc/+*+OX (n = 10) neurons.

**Figure S20. Effects of physiologic compensation in *ApcWT*+control and *ApcPirc/+*+OX neurons. a, b,** Representative fast ramp-hold-release (left, 3 mm at 20mm/s) trial from a proprioceptive neuron recorded from dorsal roots in *in vivo* electrophysiological experiments of *ApcWT*+control (grey **a**) and *ApcPirc/+*+OX rat (purple **b**). Corresponding action potential trains and overlaid black circles indicate individual action potentials (spikes) and IFRs (instantaneous firing rates) of the responses. Dashed line marks the point of muscle stretch from background length (L0) and indicates the starting point for threshold/sensitivity measurements. Boxes indicate dynamic (dark grey, 150 ms duration after stretch command onset) and static phases for analysis (light grey, 1 s duration after the dynamic phase). Stretch evoked (3mm) responses recorded from replicate trials at 1, 2, and 3x Lo for *ApcWT*+control (**a**) and *ApcPirc/+*+OX **(b). c,** Raster plots of stretch evoked (3mm) responses from representative neurons in control (right) and *ApcPirc/+*+OX(left) neurons recorded from repeated trials (4 trials) at 1, 2, and 3x background stimulus (L0 strain) intensity. Frequency histograms show cumulative distributions across 4 trials. **d,** Overlaid interval histogram (four trials per neuron at each of three stimulus intensities shows population shift. Inset show non-overlaid interval histograms for clarity. \* indicates statistically significant differences between experimental groups as empirically derived from hierarchical Bayesian model (*stan\_glm*): 95% highest density intervals do not overlap between groupwise contrasts.

**Figure S21. Cancer and chemotherapy interaction does not lead to electrophysiological evidence of degeneration.** **a,** raw intracellular record from control and *ApcPirc/+*+OX neurons shows derivation of conduction delay (ms). Conduction delay is calculated by subtracting the time from electrical stimulus to electrically evoked action potential. **b, m**ean conduction delay (ms) computed for all neurons as a measure of axonal demyelination were analyzed from *ApcWT*+control (n = 11), *ApcWT*+OX (n = 19), *ApcPirc/+*+control (n = 20) and *ApcPirc/+*+OX (n = 10) neurons with hierarchical Bayesian ANOVA model. ns, no significant difference. **c & d,** two representative stretch evoked responses of two sensory neurons (*ApcPirc/+*+OX) recorded from dorsal roots in *in vivo* electrophysiological experiments with corresponding action potential trains. Overlaid black circles are IFRs of the responses. Insets show expanded view from **(d)** in a trial without (**d1**) and with (**d2**) superimposed vibration stimulus.

**Movie S1.** Uneven ladder walking of an *ApcWT*+control rat.

**Movie S3.** Uneven ladder walking of an *ApcPirc*/++control rat.

**Movie S3.** Uneven ladder walking of *ApcPirc/+*+OX rats. Notice errors in secure forefoot (left panel) and hindfoot (right panel) placement.