Protection against oxaliplatin-induced mechanical and thermal hypersensitivity in Sarm1−/− mice

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting side effect of cancer treatment, often associated with degeneration of sensory axons or their terminal regions. Presence of the slow Wallerian degeneration protein (WLD), or genetic deletion of sterile alpha and TIR motif containing protein 1 (SARM1), which strongly protect axons from degeneration after injury or axonal transport block, alleviate pain in several CIPN models. However, oxaliplatin can cause an acute pain response, suggesting a different mechanism of pain generation. Here, we tested whether the presence of WLD or absence of SARM1 protects against acute oxaliplatin-induced pain in mice after a single oxaliplatin injection. In Bl/6 and Wld mice, oxaliplatin induced significant mechanical and cold hypersensitivities which were absent in Sarm1−/− mice. Despite the presence of hypersensitivity there was no significant loss of intraepidermal nerve fibers (IENFs) in the footpads of any mice after oxaliplatin treatment, suggesting that early stages of pain hypersensitivity could be independent of axon degeneration. To identify other changes that could underlie the pain response, RNA sequencing was carried out in DRGs from treated and control mice of each genotype. Sarm1−/− mice had fewer gene expression changes than either Bl/6 or Wld mice. This is consistent with the pain measurements in demonstrating that Sarm1−/− mice have fewer mechanical pain thresholds. In addition, DRGs associated with mechanical pain in Bl/6 mice contained significantly fewer transcripts – Alas2, Hba-a1, Hba-a2, and Tfr – correlated with oxaliplatin-induced pain, or absence thereof, across the three genotypes. Our findings suggest that targeting SARM1 could be a viable therapeutic approach to prevent oxaliplatin-induced acute neuropathic pain.

1. Introduction

Ongoing pain caused by chemotherapy-induced peripheral neuropathy (CIPN) worsens quality of life of in patients undergoing chemotherapy (Farquhar-smith, 2016). This makes CIPN a common dose-limiting side effect of diverse chemotherapeutic agents. Oxaliplatin, used against most solid cancers, causes a distal dose-dependent symmetrical ‘glove and stocking’ type painful sensory neuropathy, comprising numbness, tingling and burning sensations (Chiorazzi et al., 2015; Kanat et al., 2017). Acute, transient neuropathies manifest in 90% of patients within 24–48 h of oxaliplatin infusion (Cersosimo, 2005; Starobova and Vetter, 2017) with symptoms exacerbated by exposure to cool temperatures (Argyriou et al., 2013).

Studies in patients and animal models implicate axonal degeneration as a common process in CIPN pathology (Fukuda et al., 2017), where chemotherapeutic drugs directly or indirectly trigger a ‘dying back’ axon degeneration that progresses in a distal-to-proximal manner. This type of programmed axon death also occurs after acute injury (Waller, 2015).
2. Material and methods

2.1. Animals

All animal work was undertaken at the Babraham Institute in accordance with the Animals (Scientific Procedures) Act 1986 under project licence number 70/7620. Wild-type C57BL/6J (BL/6), Wildδ and Sarm1−/− male mice (both on a C57BL/6J background) aged 12–16 weeks were used for the study. Mice were housed under controlled conditions (12 h light-dark cycle) in individually ventilated cages (IVCs) in a pathogen-free environment with standard rodent chow and water available ad libitum (except when behavioural assessments were being made). Most mice were group housed (2–3 mice per cage), though very occasionally a mouse was housed individually.

2.2. Oxaliplatin administration

We assessed behaviour and intraepidermal nerve fiber (IENF) density after administration of a single intraperitoneal (i.p.) 6 mg/kg oxaliplatin injection as previously described (Descoeur et al., 2011; Young et al., 2014), outlined in Supplementary Fig. 1. Oxaliplatin (Sigma-Aldrich) was dissolved in 0.9% sodium chloride (AppliChem).

2.3. Behavioural tests

Mechanical allodynia was assessed using a dynamic plantar aesthesiometer and thermal allodynia using a dynamic cold plate. For the plantar aesthesiometer test, mice were placed into individual sections of a plastic box with a wire mesh floor and left to habituate for 30–60 min. Then, a dynamic plantar aesthesiometer (Ugo Basile) was used to apply pressure up to a maximum of 5 g at a rate of 0.5 g/s to the plantar region of the right hind paw. If the mouse did not withdraw its paw after 30 s, the experiment was stopped manually and the probe retracted. This was repeated five times with at least 10 min between each measurement. The average of the five values for each mouse was taken forward for analysis. This was repeated 48 h after oxaliplatin administration. For the cold plate test, an individual mouse was placed onto a dynamic hot/cold plate (Ugo Basile) at 18 °C. The plate was cooled at a rate of 0.3 °C/min to 2 °C and the number of jumps (defined as both rear paws off the plate simultaneously) was recorded and grouped into 2 °C bins (Young et al., 2014). The baseline measurement is the number of jumps prior to oxaliplatin injection. This process was repeated 4 days after mice received the injection to obtain the post-oxaliplatin measurements, based on a previous study which noted that cold sensitivity peaked 4 days after oxaliplatin administration (Young et al., 2014). We refer to this as allodynia (rather than hyperalgesia) since in our mice, no increase in jumping behaviour was observed at lower temperatures before oxaliplatin administration, suggesting these temperatures are not painful in naïve mice. Cold plate data is presented as the area under the curve alongside individual time courses.

2.4. Sample sizes and exclusions

In all behavioural studies, group sizes were 12 mice. Control vehicle-treated groups were also included. No wild-type or Sarm1−/− mice were excluded from any of the studies. One Wildδ mouse was excluded from the study as it performed abnormally in the cold plate test at baseline compared to the other mice. The mouse was excluded from all successive assessments (including other behavioural tests and histological assessment of intraepidermal nerve fiber density).

2.5. Epidermal nerve fiber analysis

Evaluation of intraepidermal innervation (IENF) was performed using immunohistochemical staining for PGP 9.5, a pan-axonal marker, as described previously (Melli et al., 2006). Briefly, 4 days post-injection, 2 mm punch biopsies were taken from the medial footpads of the right hind limb and fixed in PLP fixative. After cryosectioning, the slides were stained with anti-PGP 9.5 antibody (Sigma-Aldrich A85925). IENFs were counted in 4–6 sections for each mouse and averaged. The data were presented as the mean number of fibers per linear millimetre of epidermis.

2.6. RNA Sequencing

2.6.1. Animals

Mice of three experimental genotypes (C57BL/6J, Wildδ and Sarm1−/−; n = 8 animals per genotype) were processed for transcriptomic studies. Two-month-old mice were administered either a
single intraperitoneal injection of 6 mg/kg oxaliplatin or saline (n = 4 mice per treatment).

2.6.2. RNA isolation
Dorsal root ganglia (L3-L5) were sub dissected in RNase-free conditions (RNaseZap, Sigma Aldrich) from freshly culled mice and flash frozen until further use. For RNA extraction, tissue was thawed directly in TRIzol reagent (Bioline) and RNA isolated following manufacturer’s instructions. RNA was purified (RNeasy kit, Qiagen) with on-column DNase treatment and analysed on an Agilent 2100 Bioanalyzer.

2.6.3. RNA-seq library preparation
Only RNA samples with RIN > 8 were used for sequencing. Libraries were prepared using the TruSeq (unstranded) mRNA kit (Illumina) following the manufacturer’s low sample protocol. Following library amplification and bead purification, the final fragment size was analysed, and libraries quantified using the Universal KAPA Library Quantification kit (Kapa Biosystems) and a Bio-Rad C100 thermal cycler. An equal amount of cDNA was used to pool up to four samples, which were sequenced in one lane. Sequencing was carried out to a depth of 20 million 25-bp single-end reads per library.

2.6.4. Bioinformatics pipeline and statistics
FastQ files were trimmed with Trim Galore v0.4.3 using default settings then aligned against the mouse GRCm38 genome assembly with hisat2 v2.0.5 using options --no-mixed and --no-discordant. Mapped positions with MAPQ values of < 20 were discarded.

Gene expression was quantified using the RNA-Seq quantification pipeline.

Fig. 1. Tactile sensitivity observed in BL/6, WldS and Sarm1−/− mice between baseline and 2 days after oxaliplatin administration. (A) Both BL/6 and WldS, but not Sarm1−/− mice exhibit increased mechanical hypersensitivity when pressure was applied to the paw using the plantar aesthesiometer. Statistically significant difference between groups is indicated (**p < 0.01, ***p < 0.001, two-way ANOVA followed by Sidak’s post-hoc pairwise comparison). (B) Mean difference in mechanical hypersensitivity between baseline and 2 days post-oxaliplatin treatment for the three genotypes. P values are shown on the graph, with statistically significant difference for BL/6 and WldS (paired t-tests followed by Bonferroni correction for multiple comparisons). Data are presented as mean ± s.e.m. n = 12 per group.
pipeline in SeqMonk v1.37.0 in unstranded library mode using gene models from Ensembl v67. For count based statistics, raw read counts over exons in each gene were used. For visualization and other statistics, log2 RPM (reads per million reads of library) expression values were used.

Differentially expressed genes were selected using pairwise comparisons with DESeq2 with a cut-off of \( P < 0.05 \) following multiple testing correction. A secondary intensity filter akin to a dynamic fold-change filter was applied to DESeq2 hits. DESeq2 comparisons were between saline and oxaliplatin treated mice of each experimental genotype.

2.7. Statistical analysis

Microsoft Excel was used to store raw data and calculate mean values. Statistical analysis and graphical visualisations were made using GraphPad Prism 6 (USA). For cold plate analysis, a Mann Whitney test followed by Bonferroni analysis was performed on area under the curve (AUC) data. For the plantar aesthesiometer, two-way ANOVA followed by Sidak’s multiple comparison test was used (for Fig. 1.A) in order to identify and quantify differences between genotypes and/or treatment overall. For Fig. 1.B, mean difference in mechanical hypersensitivity was analysed using paired \( t \)-tests followed by Bonferroni correction for

![Graphs showing statistical analysis](image-url)

Fig. 2. Oxaliplatin-induced cold hypersensitivity is prevented by removal of SARM1, but not the presence of WLD\(^s\). (A) Number of jumps made by BL/6, Wld\(^s\) and Sarm1\(^{−/−}\) mice in response to a cold ramp (cooling from 18 °C to 2 °C) before (baseline) and 4 days after a single dose of oxaliplatin. (B) BL/6 and Wld\(^s\) mice exhibit a significant increase in the number of jumps after oxaliplatin treatment while there is no change in Sarm1\(^{−/−}\) mice. Statistically significant difference between groups is indicated (*\( p < 0.05 \) and **p < 0.001, AUC-area under the curve showing difference in the total number of jumps in response to declining temperature ramp from 18 °C to 2 °C). Data are presented as mean ± s.e.m. n = 12 per group.
multiple comparisons. For assessment of intraepidermal nerve fiber density, two-way ANOVA followed by Sidak’s multiple comparison test was used.

3. Results

The present study has assessed thermal and mechanical allodynia (tested on different days to minimise interference between testing sessions; Supplementary Fig. 1) and intraepidermal nerve fiber (IENF) density after a single administration of oxaliplatin in vivo. Changes to RNA expression were also assessed after oxaliplatin administration.

3.1. Sarm1 deletion blocks the development of mechanical hypersensitivity following acute oxaliplatin treatment

In order to assess whether absence of SARM1 or presence of WLD<sup>Δ</sup> protects against mechanical allodynia, following acute oxaliplatin treatment, we injected all three mouse genotypes with a single dose of oxaliplatin (6 mg/kg). Forty-eight hours after oxaliplatin administration, wild-type and WLD<sup>Δ</sup> mice displayed increased sensitivity to pressure; they withdrew their paws at a significantly lower pressure than they did at baseline assessment (Fig. 1.A, B). Remarkably, the Sarm1<sup>−/−</sup> mice displayed no significant difference in sensitivity to pressure as their threshold for removing their paws was the same as baseline (Fig. 1.A, B). None of the three genotypes tested differed significantly in the pressure they withdrew their paws at baseline assessment (Fig. 1.A).

3.2. Sarm1 deletion prevents the development of cold hypersensitivity following acute oxaliplatin treatment

At baseline, there was no difference in cold-induced jumping behaviour of wild-type, WLD<sup>Δ</sup> or Sarm1<sup>−/−</sup> mice at any of the temperatures measured. However, 4 days after a single 6 mg/kg injection of oxaliplatin, wild-type mice showed significantly increased jumping compared to baseline measures (Fig. 2.A, B). Similarly, WLD<sup>Δ</sup> mice exhibited significantly increased jumping behaviour after oxaliplatin treatment compared to baseline and this increase was greater than that seen in the wild-type mice (Fig. 2.A, B). Interestingly, the jumping behaviour of Sarm1<sup>−/−</sup> did not change from baseline after oxaliplatin treatment (Fig. 2.A, B).

3.3. Acute oxaliplatin treatment does not induce intraepidermal nerve fiber (IENF) loss

There was no difference in IENF density between the three genotypes treated with saline (Fig. 3). No change in IENF density was detected for any genotypes post-oxaliplatin treatment. Although we cannot exclude highly localised effects outside the regions studied, this suggests that general axon degeneration does not underpin the pain phenotype after acute oxaliplatin administration.

3.4. RNA expression changes after acute oxaliplatin administration

To explore the mechanistic link between acute oxaliplatin treatment and differences in behaviour we collected RNA from dorsal root ganglia (DRGs) of mice treated with either saline or oxaliplatin (4 days after treatment). Mice used for the RNA sequencing study exhibited similar levels of mechanical allodynia as those used in the behavioural and histological studies (Supplementary Fig. 2). DRGs were chosen for RNA Sequencing as they have previously been implicated in the pathophysiology of the oxaliplatin pain mechanism. We hypothesised that acute oxaliplatin treatment would induce changes in DRG gene expression that are either a consequence of pathological events or could even be part of the pathogenic mechanism in both mechanical and cold hypersensitivity observed in these animals. Transcriptomic differences between C57BL/6, WLD<sup>Δ</sup> and Sarm1<sup>−/−</sup> mice in response to oxaliplatin treatment could underlie the differences seen in pain response and the resistance of Sarm1<sup>−/−</sup> mice to cold and mechanical hypersensitivity.

Following acute oxaliplatin treatment we observed 46 differentially expressed genes in wild-type mice relative to saline treatment (Fig. 4.A). This included 26 upregulated and 20 downregulated genes. The number of differentially expressed genes in WLD<sup>Δ</sup> mice in response to oxaliplatin treatment was lower with a total of 4 upregulated and 9 downregulated genes (Fig. 4.A). Consistent with the absence of significant behavioural changes, only three differentially expressed genes were noted in Sarm1<sup>−/−</sup> mice following treatment with oxaliplatin (Fig. 4.A) and these genes were not shared with either C57BL/6 or WLD<sup>Δ</sup> mice (Fig. 4.B). This lack of transcriptomic perturbation in Sarm1<sup>−/−</sup> mice is in keeping with their resistance to oxaliplatin-induced mechanical and cold hypersensitivity. Decreased expression of four transcripts correlated with oxaliplatin-induced pain across the three genotypes: Alas2, Hba-a1, Hba-a2, and Tfrc. (Fig. 4.C).

4. Discussion

Here, using a previously described protocol (Young et al., 2014), we report that acute oxaliplatin administration induces mechanical and cold hypersensitivities in wild-type (BL/6) and WLD<sup>Δ</sup> mice. This reflects acute peripheral neuropathies comprising cold-induced paraesthesia, dysesthesia and pain that appear abruptly after administration in the clinic (Cersosimo, 2005). We associate acute oxaliplatin-induced pain with a plethora of transcriptional changes without loss of intraepidermal nerve fibers (IENFs) in BL/6 and WLD<sup>Δ</sup> mice. Genetic deletion of Sarm1 prevents development of these acute painful neuropathies and transcriptional changes are largely absent in DRGs from Sarm1<sup>−/−</sup>-oxaliplatin-treated mice. The lack of detectable IENF loss in any genotype, and the absence of protection against pain in WLD<sup>Δ</sup> mice suggest a mechanism of pain generation independent from programmed axon death. In support of this, no known genes involved in programmed neuron or axon death were identified through our RNA sequencing. The common transcriptional changes occurring in mice that developed pain were downregulation of four iron metabolism and haem synthesis genes: Alas2, Hba-a1, Hba-a2, and Tfrc. A full list of gene expression changes observed in each genotype can be viewed in Supplementary Table 1.

While Alas2, Hba-a1, Hba-a2, and Tfrc have known functions in erythrocytes, the absence of altered erythropoiesis-specific gene expression, GATA binding protein 1 (Gata1) and erythroid-associated factor (Erα), or endothelial specific genes, CD34 and Vascular Endothelial Growth
Factor Receptor 2 (KDR), indicate that differential gene expression was not due to contamination by erythrocytes (Richter et al., 2009; Vanni et al., 2018). Interestingly, literature describes roles of ALAS2 and haemoglobin in central and peripheral neurones, including DRGs (Biagioli et al., 2009; Haraguchi et al., 2011; Richter et al., 2009; Stephens et al., 2019; Walser et al., 2017). Genetic mutations in Alas2, haemoglobin, and Tfrc genes have been observed in patients with painful or neurodegenerative conditions (Bishop et al., 2013; Kallianpur et al., 2014; Vanni et al., 2018): Haemoglobin in human brain (Biagioli et al., 2009; Richter et al., 2009) is differentially expressed in frontal cortex of humans with prion-related neurodegenerative diseases (Vanni et al., 2018). Mouse models of depression and chronic stress exhibit increased expression of Alas2 (Stankiewicz et al., 2015; Stankiewicz et al., 2014; Yamamoto et al., 2015). Animal models of pain show that chemotherapeutic paclitaxel causes downregulation of Hba and Hbb in rat DRGs (Nishida et al., 2008), and there is an association between chronic constriction injury-induced neuropathic pain with downregulation of Alas2, Hba-a1, and Hba-a2 (amongst other genes) in DRGs of female mice (Stephens et al., 2019). This evidence along with changes we noted in our acute OIPN model supports a role of Alas2, Hba-a1, and Hba-a2 downregulation in painful neuropathies. However, whether these are causal or reflect other pathogenic events is a crucial question for future studies to address.

Oxaliplatin accumulates in rat DRG mitochondria (Nishida et al., 2018) causing downregulation of mitochondrial electron transport chain proteins and increased reactive oxygen species (ROS) which is associated with oxaliplatin-induced mechanical allodynia (Cheng et al., 2019). Since Alas2, Hba-a1, and Hba-a2 are important for mitochondrial function, their downregulation could indicate mitochondrial stress. Indeed, mitochondrial toxin rotenone causes transcriptional downregulation of neuronal haemoglobin genes Hba-a2 and Hbb in rats (Richter et al., 2009). Removal of SARM1 protects against axon degeneration triggered by mitochondrial toxins rotenone and CCCP (Loreto et al., 2020; Summers et al., 2014) and sub-degenerative concentrations of CCCP induce SARM1 activation without causing degeneration (Sasaki et al., 2020). Taken together, we speculate that removal of SARM1 could protect against oxaliplatin-induced mitochondrial dysfunction associated with SARM1 activation in a context that leads to pain in the absence of axon degeneration.

Oxaliplatin forms protein adducts with many proteins (Graham et al.,

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**Fig. 4.** RNA Sequencing identified common genes downregulated in BL/6 and Wlds mice that were not differentially expressed in Sarm1+/− mice. (A) M (log ratio)–A (mean average) plots of significantly differentially expressed genes (DEGs) in DRGs of BL/6, Wlds and Sarm1+/− mice after treatment with oxaliplatin (RPM, reads per million reads of input). Comparison: DESeq2 (differential gene expression analysis based on negative binomial distribution) saline vs. oxaliplatin treatment (n = 4 mice per treatment per genotype). Blue dots indicate significant changes (DESeq2) and red dots indicate significant changes that are also intensity hits. (B) Venn diagram highlighting overlapping DEGs between BL/6, Wlds and Sarm1+/− mice after treatment with oxaliplatin. (C) Common DEGs in BL/6, and Wlds mice following oxaliplatin treatment are highlighted. All differentially expressed genes are listed in Supplementary Table 1.
2000; Pendyala and Creaven, 1993) and oxaliplatin-haemoglobin adducts have been shown to affect cytoplasmic pH and sensitize TRP channels in DRGs (Peng et al., 2005; Potenzieri et al., 2020). Activation of TRP channels is associated with pain (Jang et al., 2018), including oxaliplatin-induced mechanical allodynia (Sakurai et al., 2009), and mice lacking TRPM2 exhibit decreased mechanical allodynia after paclitaxel (So et al., 2017; Horsefeld et al., 2019) can activate the TRPM2 channel (Yu et al., 2019). Therefore, another speculative pathway through which SARM1 may act in pre-degeneration pain pathophysiology could be TRP channel activation or sensitisation via SARM1 products.

Finally, SARM1 is also reported as a positive regulator of cytokine and chemokine production in the innate immune system (Hou et al., 2013; Szeret et al., 2018; Wang et al., 2018). Acute oxaliplatin treatment increases C–C chemokine ligand 2 (CCL2) in small rat DRGs whereas its receptor (CCR2) is increased in medium and large DRGs, associated with mechanical hypersensitivity (Illias et al., 2016). However, a recent study questions the extent to which SARM1 is truly involved in mediating cytokine responses (Uccellini et al., 2020) and no altered chemokine RNA transcripts were associated with acute oxaliplatin administration in the present study. However, the heterogeneity of our DRG population could confound our ability to detect altered transcription that may occur in specific DRG sub-types, of which there are 11 possessing distinct mRNA profiles (Li et al., 2016; Usoskin et al., 2015).

5. Conclusions

The present study contributes data towards an emerging role of Alas2, Hba-a1, and Hba-a2 gene downregulation in pain pathophysiology and a role of SARM1 in acute chemotherapy-induced peripheral neuropathy. This work raises several interesting questions which future studies should address, including: Do these gene expression changes drive pain pathophysiology or are they a consequence of mitochondrial dysfunction or other pathological changes? What role does SARM1 activation have in the absence of programmed axon death? Are other axonal proteins such as tubulin or pro-survival protein NMNAT2 modified in the presence of oxaliplatin and do they play a causative role in CIPN?

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Declaration of Competing Interest

None.

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