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Neurotoxicity to DRG neurons varies between rodent strains treated with cisplatin and bortezomib

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose limiting side effect that can lead to long-term morbidity. Approximately one-third of patients receiving chemotherapy with taxanes, vinca alkaloids, platinum compounds or proteasome inhibitors develop this toxic side effect. It is not possible to predict who will get CIPN, however, genetic susceptibility may play a role. We explored this hypothesis using an established *in vitro* dorsal root ganglia neurite outgrowth (DRG-NOG) assay to assess possible genetic influences for cisplatin- and bortezomib-induced neurotoxicity. Almost all previous *in vitro* studies have used rats or mice. We compared DRG-NOG between four genetically defined, inbred mouse strains (C57BL/6 J, DBA/2 J, BALB/cJ, and C3H/HeJ) and one rat strain (Sprague Dawley). Our studies found differences in cisplatin and bortezomib-induced neurotoxicity between mouse and rat strains and between the different mouse strains. C57BL/6 J and Balb/cJ DRG-NOG was more sensitive to cisplatin than DBA/2 J and C3H/HeJ DRG-NOG, and all mouse strains were more sensitive to cisplatin than rat. Bortezomib induced a biphasic dose response in DBA/2 J and C3H/H3J mice. C57BL/6 J DRG-NOG was most sensitive and Balb/cJ DRG-NOG was least sensitive to bortezomib. Our animal data supports the hypothesis that genetic background may play a role in CIPN and care must be taken when rodent models are used to better understand the contribution of genetics in patient susceptibility to CIPN.

1. Introduction

The genealogy of the laboratory mouse has been well documented with most strains of inbred mice originating from the colony of Abbie Lathrop [1]. These mice were distributed and independent inbred colonies were generated around the world. A mouse strain is considered inbred when it has been bred brother to sister for 20 generation and can be traced back to one breeder pair at the 20th or subsequent generation (Goios et al., 2007). Outbred mice, on the other hand are a closed population of mice maintained for high heterozygosity for at least four generations [2]. Despite a common inbred mouse ancestry, significant genome sequences and their genetic variations have been found and cataloged in 17 different mouse strains from various inbred colonies. Next-gen sequencing found a total of 56.7 M single nucleotide polymorphisms (SNPs), approximately 9.45 M small insertions and deletions and 711,920 structural variations within the different mouse strains [3]. MtDNA sequencing confirmed a high sequence similarity consistent with a common female ancestor, with 15 base substitutions between 11 mouse strains sequenced [4]. Genetic variability between mouse strains in combination with genetic homogeneity within mouse strains makes inbred mice good models to study genetic influences on drug response.

Genetic variations between mouse strains can influence response to drug treatment and is associated with different behavioral phenotypes. In streptozotocin (STZ) treated mice, genetic strain variations showed a significant difference in renal injury. DBA/2 J and KK/H1J mice showed significantly greater renal injury then C57BL/6 J, AJ and MRL/MpJ mice [5]. In models of chemotherapy-induced neurotoxicity, differences in behavior responses were observed between paclitaxel treated mouse strains. Ten different mouse strains were exposed to paclitaxel for 7 days and tested for mechanical allodynia using the Von Frey assay. DBA/2 J mice with high response and C57BL/6 mice with low response to paclitaxel treatment were further studied for thermal hyperalgesia and cold allodynia. DBA/2 J had a significantly longer response time than C57BL/6 J when tested for response to heat, however, there was no difference in response to cold [6].

Chemotherapy induced peripheral neuropathy (CIPN) is a serious side effect of cancer treatment for many patients and can affect long-term quality of life. Cisplatin and bortezomib are effective agents for the treatment of germ line cancers and multiple myeloma that induce peripheral neuropathy in 20–40% of patients. Peripheral neuropathy is

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linked to the cumulative dose of cisplatin administered to patients and for bortezomib development of neuropathy appears to be dose-related [7]. It has been reported that patients with mild or subclinical inherited neuropathies have exaggerated neurotoxic responses to chemotherapy drugs [8]. However, it is not well understood why some patients get neuropathy while others do not.

In experimental models, the mechanisms of neurotoxicity appear to be different between cisplatin and bortezomib. Cisplatin kills dorsal root ganglion (DRG) neurons, *in vitro*, by binding both nuclear and mitochondrial DNA, inducing DNA damage and apoptosis [9–15]. Bortezomib inhibits proteasome function, in cultured DRG neurons, inducing accumulation of polymerized tubulin and inhibition of mitochondrial axonal transport [15]. Both cisplatin and bortezomib have also been shown to have significant effects on the mitochondria. Cisplatin binds to mtDNA inhibiting mtDNA replication and transcription leading to mitochondrial vacuolization and degradation, *in vitro* and *in vivo* [14]. Bortezomib has been shown to induce deficits in mitochondrial complex I and II function and significantly decreased ATP production *in vivo* [16]. None of these studies have looked at genetic variation in relationship to developing CIPN.

Measurement of neurite outgrowth (NOG) from embryonic DRG neurons *in vitro* is an established model to study the neurotoxic effects of various agents including chemotherapy drugs and can be used for genetic screens. [11–14,17–19]. It is a rapid and reproducible way to look at general neurotoxicity of compounds. Our studies were designed to look at the effects of cisplatin and bortezomib on NOG and determine whether genetic variations between mouse strains would alter the sensitivity of the DRG neurons.

2. Materials and methods

2.1. Animals

A total of 25 timed-pregnant mice from 4 strains, C57BL/6 J, DBA/2 J, BALB/cJ, and C3H/HeJ (Jackson Laboratory, Bar Harbor, ME) and 3 timed pregnant Sprague Dawley rats (Harlan, Indianapolis, IN) were used for the experiments. All animal studies were in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care International. Mouse strains were chosen from different hereditary lineages and NOG compared to each other as well as compared to the rat model we routinely use in our laboratory (Fig. 1).

2.2. Surgical procedure

On embryonic day 13, timed pregnant female mice were anesthetized with sodium pentobarbital. E-13 mouse embryos were removed from the uterus and placenta then placed into L-15 medium (Life Technologies, Grand Island, NY). The pups were euthanized by decapitation and the spinal column was removed using a dissecting microscope (Carl Zeiss, Jena, Germany). Dorsal root ganglia (DRG) attached to the spinal cord cervical, thoracic, lumbar and sacral segments were removed and placed into a separate dish. 30–40 DRG were isolated from each pup. All surgical procedures were performed using aseptic precautions and sterile technique under a laminar flow clean hood. Embryonic day 15 rat pups were processed in the same manner.

2.3. Cell culture

Whole DRG explants were cultured on 35-mm collagen coated, plastic dishes with AN2 medium (MEM plus 10% calf bovine serum, 200 mM L-glutamine, 20% glucose) in the presence of 10 ng/ml NGF and incubated at 37 °C. Initial plating was done in a small volume of medium for 1–2 h to allow for attachment followed by additional medium up to 1 ml.

2.4. Neurite outgrowth assay

In each dish 3–4 DRGs were plated into AN2 medium media with or without 1, 5, 10, and 50 μg/ml cisplatin or 25, 50, 100 and 200 nM bortezomib. Each rodent strain had 3–4 replicate dishes with a total of 17–35 DRG explants per condition. Cultures were incubated for 48 h at 37 °C. NOG was evaluated by acquiring images using a Nikon digital camera (Nikon, Melville, NY) and measuring the length of the longest neurite of each DRG using ImageJ software (NIH, Bethesda, MD, USA) at 48 h [18,19]. Shown are images of neurite outgrowth of rat, C3H/HeJ and C57BL/6 J DRG neurons under control conditions, (Fig. 2A, B, G) treated with 5 μg/ml cisplatin (Fig. 2C, D, E) or 50 nM bortezomib (Fig. 2E, F).

2.5. Data analysis and statistics:

Data was analyzed and graphed using Prism Software (Graph Pad, La Jolla, CA). Statistical analysis was done using one way ANOVA and Bonferroni's multiple comparisons test. To calculate the half maximal inhibitory concentration (IC50), the dose response curve of cisplatin

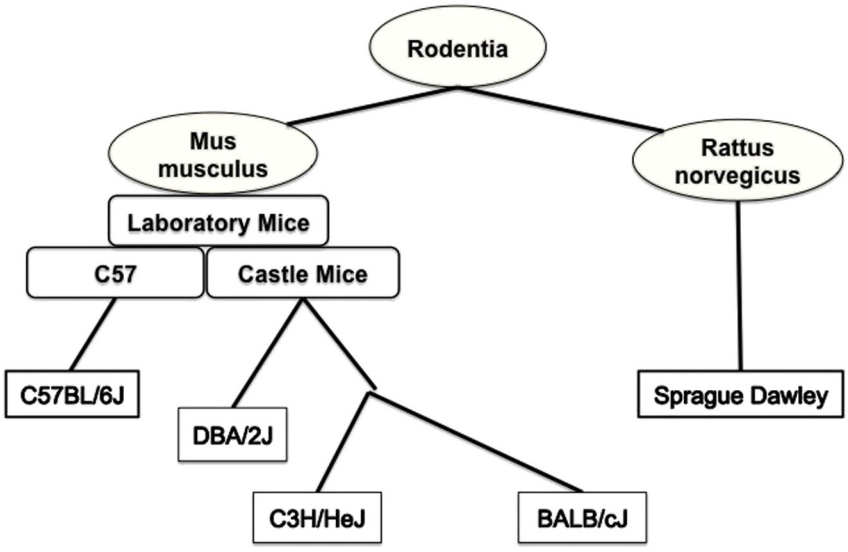

Fig. 1. Diagram of the genetic relationship between different mouse strains and rat. Abby Lathrop from 1903 to 1915 bred mice from which the C57 related and Castle mouse lines were generated. DBA/2 J, C3H/HeJ and Balb/cJ are different strains derived from the Castle mouse line and C57BL/6 J are from the C57 related line [1]. Sprague Dawley Rats are a common outbred laboratory rat developed by the Sprague Dawley Animal Company (Madison, WI).

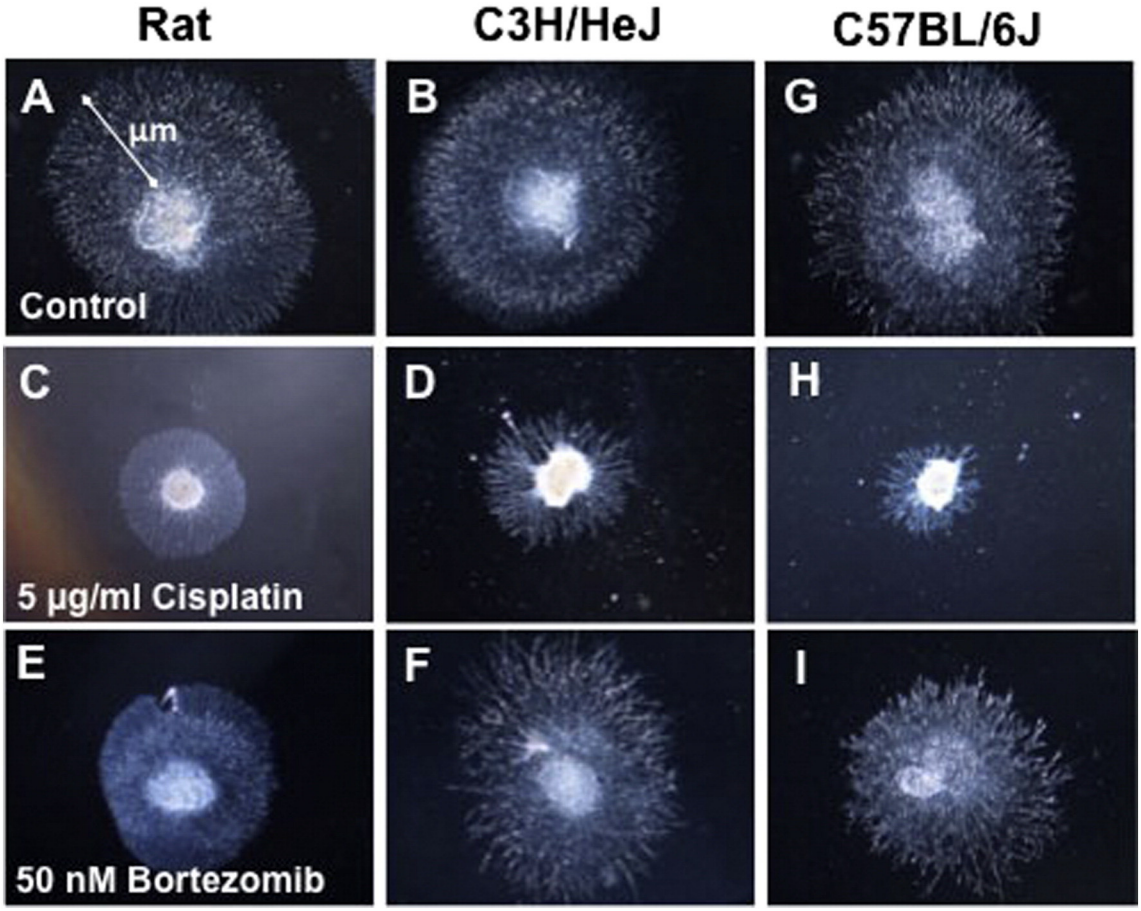

Fig. 2. Neurite outgrowth of rat, mouse C3H/HeJ and mouse C57BL/6 J DRG under control conditions (Fig. 2A–C), treated with 5 μg/ml cisplatin (Fig. 2 C–H) and 50 nM bortezomib (Fig. 2 E–I). NOG is measured from the outside edge of the DRG to the longest neurite length and expressed in μm (white arrow).

was transformed and expressed as a percent inhibition of neurite outgrowth and the log of the concentration. Quantitation of IC50 was done using non-linear regression-log agonist *vs.* normalized response of neurite outgrowth inhibition.

3. Results:

3.1. Cisplatin on NOG

Cisplatin inhibited NOG in a dose dependent manner. DRG neurons were treated with 0, 1, 5, 10 and 50 μg/ml cisplatin for 48 h and measured for the longest neurite length. Dose response curves for cisplatin treated DRG-NOG were plotted as a log of concentration (Fig. 3A). Significant differences in NOG were observed at 1 ($p < 0.05$-$p < 0.0001$), 5 (black arrow, $p < 0.05$-$p < 0.001$) and 10 μg/ml ($p < 0.01$–0.001) cisplatin. No significant difference was observed with 50 μg/ml cisplatin. At 5 μg/ml cisplatin, closer observation showed that rat DRG-NOG was significantly longer than C57BL/6 J ($p < 0.001$) and Balb/cJ ($p < 0.05$) DRG-NOG (Fig.3B). DRG-NOG in rat was 625 μm (SEM, 47), C57BL/6 J was 408.9 μm (SEM, 21) and Balb/cJ was 455.6 μm (SEM, 20). Significant differences were also found between C57BL/6 J and C3H/HeJ DRG-NOG ($p < 0.01$) with DRG-NOG in

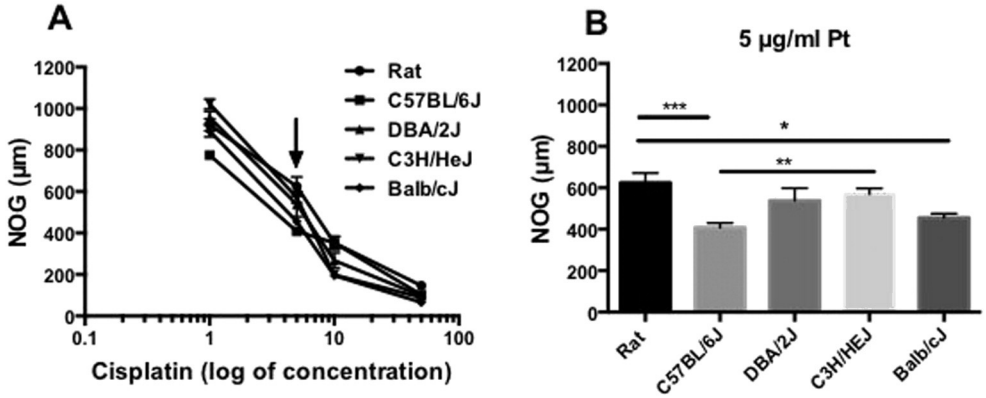

Fig. 3. (A) Cisplatin dose response curve plotted as a log of concentration. At 1, 5 (black arrow) and 10 μg/ml cisplatin, differences in DRG-NOG can be seen between strains. Comparison of rat and mouse DRG-NOG at (B) 5 μg/ml cisplatin showed significant differences between rat and C67BL6/J mouse DRG NOG ($p < 0.001$), rat and Balb/cJ DRG-NOG ($p < 0.05$) and C57BL6/J and C3HHE/J mouse DRG-NOG ($p < 0.01$).

C3H/H3J, 571 μm (SEM, 27). There was no significant difference in DRG-NOG between mouse strains or rat under control non-drug treated conditions.

3.2. Bortezomb on NOG

Bortezomib had different effects on DRG-NOG between rodent strains. Dose response curves of bortezomib treated DRG-NOG were plotted as log of concentration (Fig. 4A). DRG were treated with 25, 50 (black arrow), 100 and 200 nM bortezomib. Bortezomib induced inhibition of DRG-NOG in a dose dependent manner for all strains except DBA/2 J and C3H/HeJ mouse DRG. In DBA/2 J and C3H/H3J DRG, bortezomib had a biphasic effect with an increase in DRG-NOG at 25 and 50 nM followed by a decrease in DRG-NOG at higher concentrations. DBA/2 J DRG-NOG increased from 0 nM, 855.9 μm (SEM, 34.7) to 25 nM, 1228 μm (SEM, 33) bortezomib and decreased when the concentration of bortezomib was increased to 50 nM, 1170 μm (SEM, 31.1). DRG-NOG in C3H/H3J mouse, increased between 25 nM, 1003 μm (SEM, 27.8) and 50 nM, 1054 μm (SEM, 35) followed by decrease in DRG-NOG at 100 nM, 781.9 μm (SEM, 78.6). Closer observation of DRG-NOG at 50 nM bortezomib between rat and mouse DRG-NOG (Fig. 4B) showed DBA/2 J and C3H/HeJ had significantly longer DRG-NOG ($p < 0.0001$) than rat DRG-NOG, 744 μm (SEM, 30.9). There was no significant difference between rat and C57BL/6 J, 710 μm (SEM, 67.4), or Balb/cJ, 902.2 μm (SEM, 42.6), DRG-NOG. DBA/2 J and C3H/HeJ DRG also had longer NOG than C57BL/6 J mouse ($p < 0.0001$) and DBA/2 J had longer DRG-NOG than Balb/cJ ($p < 0.01$).

3.3. IC50 of cisplatin and bortezomib

The IC50 indicates that Balb/cJ DRG-NOG is most sensitive to cisplatin and DBA2J DRG-NOG is the most resistant to cisplatin (Table 1). All mouse strains were more sensitive to cisplatin than rat DRG-NOG. With respects to Bortezomib C57BL/6 J DRG-NOG is most sensitive and Balb/cJ DRG-NOG is most resistant to bortezomib.

Table 1
The IC50 for rat and each mouse strain was calculated using the non-linear regression-log agonist *vs.* normalized response of neurite outgrowth inhibition.

Species strain	IC50 cisplatin (μg/ml)	IC50 bortezomib (nM)
Rat Sprague Dawley	7.4	176.7
Mouse C57BL/6 J	5.8	134.1
Mouse DBA/2 J	6.5	177.0
Mouse C3H/HeJ	5.5	178.1
Mouse Balb/cJ	5.0	255.9

4. Discussion

Rodents are important experimental models for understanding the mechanism of CIPN. Rodents of different species or strains have been used extensively to study CIPN *in vivo* and *in vitro*, with little attention to strain differences. Transgenic mice are important tools for determining the role of a gene in CIPN mechanism [20]. Rats are good models for the study of nerve conduction velocities and behavior in relation to CIPN [21]. Both rat and mouse DRG can be used *in vitro*, however, we have found significant differences in how sensitive they are to cisplatin and bortezomib. We also found significant differences in response to drug between the different mouse strains. When designing experiments our study shows it is important to do independent drug dose response curves for each rodent strain and use matching genetic backgrounds. It is also important to determine if outbred or inbred mice should be used for a study. Outbred mice are better for studies that are designed to study the effect of a drug on a more heterogeneous genome. The effects of individual genetic variations are better studied in inbred mice where the background is controlled.

Our studies looked at four different mouse strains, one the C57 related line and three from the Castle Mice line. This allowed us to look at DRG-NOG response between less related and closer related mouse strains. Castle mice used in our experiments, DBA/2 J, C3H/HeJ and Balb/cJ mice, were derived from C. C. Little's laboratory. DBA/2 J mice are a colony derived from Sub-line 212 and C3H/HeJ and Balb/cJ mice are different sub-stocks derived from Stock D. We made the assumption that the more closely related mice would be more similar in their genetic makeup and in their response to drugs. C3H/HeJ and DBA2J were not significantly different in their response to either cisplatin or bortezomib. However, there were significant differences in drug response between Balb/cJ and the other two Castle strains. Balb/cJ mice were bred through two more stock transitions (Stock A and then Stock B) and may be more genetically different from C3H/HeJ and DBA/2 J mice. C57BL/6 J mice derived from a different mouse colony had a significantly different response to cisplatin and bortezomib than C3H/HeJ and DBA/2 J but not Balb/cJ.

Goios *et al.*, showed a high mtDNA sequence similarity between 11 different inbred mouse strains [4]. However, small sequence differences in mtDNA between C57BL/6 and C3H/H3 mice contributed to acute cardiac volume-overload sensitivity [22]. Both cisplatin and bortezomib affect the mitochondria. Pt-mtDNA adducts prevents mtDNA replication and transcription leading to mitochondrial degradation and vacuolization [14]. Bortezomib interferes with mitochondrial axonal trafficking and induces vacuolization of mitochondria in a small number of rat DRG neurons, *in vivo* [23]. Cisplatin and botezomib both lead to mitochondrial degradation, however, cisplatin results in apoptosis in DRG neurons while bortezomib does not. It is possible the difference we see in sensitivity to cisplatin and bortezomib is associated with the level of mitochondrial stress induced by the drugs.

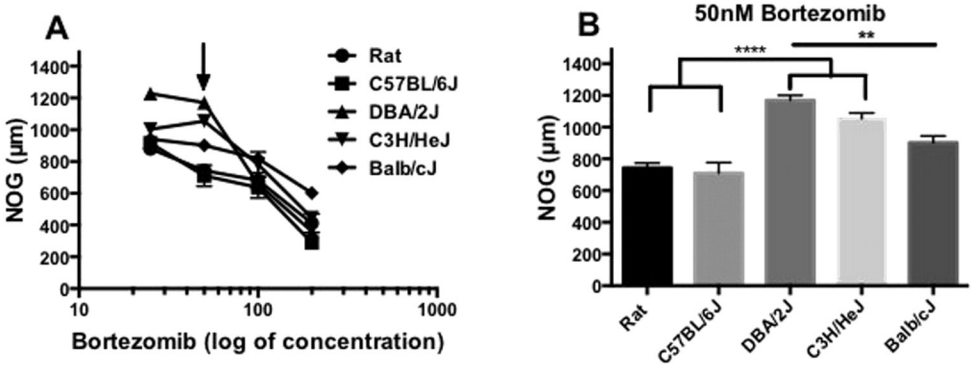

Fig. 4. (A) Bortezomib dose response curve plotted as log of concentration. Different rodent strains had different responses to bortezomib. DBA/2 J and C3H/HeJ DRG-NOG had biphasic dose response curves while rat, C57BL/6 J and Balb/cJ dose response consistently decreased. Comparison of rat and mouse DRG-NOG at (B) 50 nM bortezomib treatment showed DBA/2 J and C3HHE/J mouse DRG are less sensitive to bortezomib than rat, C57BL6/J and Balb/cJ DRG-NOG ($p < 0.01$–$p < 0.0001$).

Genetic variability in patient backgrounds may be involved in determining susceptibility to CIPN. The most common inherited neuropathy that may be present in subclinical form is Charcot–Marie–Tooth (CMT) disease which is due to duplications, deletions and mutations in at least 80 disease-causing genes [24]. Next Gen sequencing of CMT genes in non-CMT patients observed for taxol-induced CIPN showed two genes shared between the two diseases [25]. Beutler *et al*., identified heterozygous single nucleotide variants (SNV) in PRX, involved in stabilization of myelin in the peripheral nervous system and ARHGEF10, a gene involved in cytoskeleton and microtubule dynamics. In a separate study Johnson and colleagues found over-representation of polymorphisms in the glutathione peroxidase 7 (GPX7) and ATP-binding cassette sub-family C member 4 (ABCC4) genes in patients developing CIPN when treated with the combination of cisplatin and paclitaxel [26].

5. Conclusions

We found measureable differences in DRG-NOG response to cisplatin and bortezomib. In cisplatin treated DRG the IC50 of mouse DRG-NOG was lower than the IC50 of rat DRG-NOG indicating that mice overall are more sensitive to cisplatin than rat. DRG treated with 50 μg/ml cisplatin had significantly shorter neurites in C57BL/6 J and Balb/cJ mice than in rat and between mouse strains C57BL/6 J mice had significantly shorter neurites then C3H/HeJ mice. The biphasic effects of bortezomib on DRG-NOG made it more difficult to interpret the differences in IC50, however, Balb/cJ mice had a very different curve from rat and the other mouse strains and a much higher IC50 indicating they may be more resistant to bortezomib. At 50 nM bortezomib, C3H/HeJ and DBA2J DRG had significantly longer neurites than rat, C57BL/6 J and Balb/cJ DRG indicating they are more resistant to bortezomib at specific drug concentrations. Our data shows there are differences in drug response between mouse and rat and between the various mouse strains. Genetic background should be considered when setting up experimental models. It also provides additional evidence that genetic influences may be critical in determining whether individual cancer patients develop CIPN when treated with a drug.

Acknowledgments

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