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Microtubule stabilisation and mitochondrial dysfunctions as axonal degeneration mechanisms in bortezomib-treated sensory neurons

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The causal mechanisms underlying chemotherapy-induced peripheral neuropathy (CIPN) are not yet fully understood, but primary afferent neurons have emerged as a vulnerable initiating pathophysiological target. Bortezomib (BTZ) is a proteasome inhibitor, which results in axonal degeneration, producing in patients a disabling painful peripheral neuropathy that undermine its therapeutic efficacy.

In the current study, we examined whether treatment with BTZ for 24 hours would affect microtubule (MTs) stability as well as axonal transport and oxidative phosphorylation or mitochondrial bioenergetics in primary cultured dorsal root ganglion (DRG) sensory neurons. MT stability was indirectly measured by western blotting and quantitative immunofluorescence microscopy of delta2 tubulin and tubulin acetylation, while axonal mitochondrial trafficking was evaluated by time-lapse confocal microscopy and kymograph analysis. To evaluate the effects of BTZ on the generation and regulation of cellular bioenergetics, mitochondrial oxidative phosphorylation (OXPHOS) and fusion/fission balance were described via western blot analysis of key molecular markers, and real-time oxygen consumption rate (OCR), an indicator of mitochondrial respiration, was obtained by Seahorse bioanalyser.

BTZ-treated sensory neurons induced an approximately 2.5-fold increase of delta2 and acetylated tubulin levels, which occurred at the onset of axonal degeneration. Furthermore, DRG axonal mitochondrial motility was decreased by BTZ. Finally, BTZ treated DRG neurons had no differential protein expression of OXPHOS subunits compared to untreated DRG neurons, whereas increased Mitofusin-2 protein expression and bioenergetics deficits were reported.

In summary, our results provide support for the role of MT stability and mitochondrial dysfunction in the development of BTZ mediated neuropathy. Understanding these pathways may provide therapeutic targets for the treatment of this debilitating complication.

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