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OC.8-PATHOGENIC ROLE OF TUBULIN POST-TRANSLATIONAL MODIFICATIONS IN BORTEZOMIB-INDUCED PERIPHERAL NEUROPATHY (BIPN)

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Tubulin and microtubules (MTs) play critical roles in neuronal function and are well-established targets for certain anticancer drugs that can also induce chemotherapy induced peripheral neuropathy (CIPN) (vinca, alkaloids, taxanes). The contribution of these MT changes to the onset of CIPN is not well understood, but strongly predicted to be a determining factor. We hypothesized that seemingly unrelated CIPN-inducing drugs may share an underlying mechanism of pathogenesis based on acute alteration of one or more tubulin post-translational modifications (PTMs). To examine this, we measured the relative levels of selected tubulin PTMs in the cell bodies of dorsal root ganglia (DRG) and in sciatic nerves (SNs) isolated from rats treated with acute doses of the proteasome inhibitor Bortezomib (Bort) prior to any manifestation of neuronal injury or neuropathic behavior. Among the tubulin PTMs examined, delta-2 tubulin (D2), an irreversible tubulin PTM and marker of hyperstable MTs, was significantly increased in L4-L5 DRG and SNs of Bort treated rats, and high levels of D2 were further detected in the sural nerve from a cancer patient suffering from BIPN. We examined the pathogenic potential of D2 accumulation in dissociated adult DRG neurons and found that while induction of D2 alone was sufficient to cause axonopathy, reducing D2 accumulation significantly alleviated axonal degeneration promoted by Bort. Our results suggest that the mechanisms of CIPN drugs may converge on the acute perturbation of tubulin PTMs, and that disruption of the tubulin detyrosination cycle may play a role in the axonal injury induced by Bort.