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MINDS MATTER: CREATING CONNECTIONS IN NEUROSCIENCE RESEARCH

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Proteasome inhibitors-based chemotherapy-induced neurotoxicity: mitochondrial, calcium signalling and cytoskeleton alterations

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20S proteasome inhibitors bortezomib (BTZ) and carfilzomib (CFZ), approved by FDA for the treatment of multiple myeloma (MM) and other tumours, significantly improved survival of patients. However, complications, such as chemotherapy-induced peripheral neurotoxicity (CIPN), leading to the dose reduction and withdrawal from therapy, compromise clinical outcome. Although mechanisms of neurotoxicity remain poorly understood, studies show that BTZ is somewhat more neurotoxic than CFZ. Here, using primary cultures of sensory neurons, we investigated the effects of BTZ and CFZ on mitochondrial function, Ca^{2+} signalling, and cytoskeleton phenomena most associated with CIPN.
Assessment of cytosolic ($[Ca^{2+}]$cyt) and mitochondrial ($[Ca^{2+}]$mit) Ca^{2+} signals, in response to chemical depolarization (40mM KCL, 10 sec) was performed using Fura-2 and mito-Fura-2, respectively. First, we identified the regimen, equally inhibiting 20S proteasome activity (10nM BTZ; 60nM CFZ for 24h), and confirmed that, at these regimens, BTZ, but not CFZ, produces marked neurotoxic effects. Afterwards, analysis of mitochondrial functions showed that both BTZ and CFZ significantly reduced basal and induced OCR, ATP-linked respiration and mitochondrial membrane potential. Moreover, the calcium imaging results show that BTZ significantly reduced the amplitude of $[Ca^{2+}]$cyt. Assessment of mitochondrial Ca2+ signals is now in progress. Finally, analysis of post translational modifications of tubulin (the main cytoskeletal component associated with CIPN) showed that BTZ, but not CFZ, dramatically augmented levels of acetylated tubulin and delta-2-tubulin, important hallmarks of CIPN-associated neuropathy. Altogether, our results suggest that specific BTZ
induced neurotoxicity involves alterations of cytoskeleton and of Ca^{2+} fluxes through the plasma membrane, while the worsening of the bioenergetic profile may be linked to common mechanisms of anti-tumour activity.

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