

Bortezomib-Induced Peripheral Neuropathy: A Snapshot Of The Role Of Mitochondria-ER Contact Sites

Bortezomib (BTZ) is a first generation proteasome inhibitor employed against multiple myeloma that commonly induces a set of adverse effects over the peripheral nervous system (PNS) collectively known as BTZ-induced peripheral neuropathy (BIPN). BIPN clinical manifestations deeply threaten patients' quality of life, frequently leading to chemotherapy dose reduction. Despite there is no consensus regarding the pathogenesis of BIPN yet, in the last years a new hypothesis gained attention, suggesting mitochondrial dysfunction as a major player in the development of BIPN.

Based on this evidence, we first aimed at investigating the "mitochondrial hypothesis" of BIPN in MSC80, a murine cell line chosen as model for Schwann cells.

In line with studies conducted on neurons, we found that a 24h treatment with BTZ 10nM significantly depolarizes the mitochondrial membrane, however displaying milder effects towards mitochondrial respiration capacity. Surprisingly, we observed that BTZ induces a drastic rearrangement of the mitochondrial network, with evident perinuclear clustering and loss of network complexity. Additionally, we focused our attention on mitochondria-endoplasmic reticulum (ER) contact sites (MERCs), key regulatory hubs of mitochondrial homeostasis. By employing a palette of fluorescence-based dedicated sensors, we found that BTZ induces a substantial reduction (~50%) of MERCs at different distance ranges, inevitably affecting MERCs-related functions such as Ca^{2+} transfer and mitochondrial dynamics.

Meanwhile, we tried to counteract BTZ-induced alterations by employing allopregnanolone, a neuroactive steroid whose neuroprotective role, we propose, could be partially modulated at the MERCs level, and observed that it almost completely preserves the mitochondrial network/distribution and the number of MERCs.

Collectively, our preliminary results indicate that, in MSC80, BTZ-related toxicity affects mitochondria from both a functional and morphological point of view, suggesting a crucial role for MERCs at the crossroads, which, to our knowledge, is a completely novel perspective in the field of BIPN research.