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SESSION V
PERIPHERAL SYSTEM AND GUT-BRAIN AXIS

MORPHOLOGICAL AND METABOLOMIC CHANGES IN PIPN

Bonomo R[1,2], Canta A[1], Chiorazzi A[1], Carozzi VA[1], Meregalli C[1], Pozzi E[1], Alberti P[1,4], Marmiroli P[1], Skene DJ[3], & Cavaletti G[1,4]

[1]*Experimental Neurology Unit, School of Medicine and Surgery, University of Milano-Bicocca, Via Cadore 48, 20900, Monza, Italy;*
[2]*School of Medicine and Surgery, Kore University of Enna, Enna, Italy;*
[3]*Chronobiology, Faculty of Health and Medical Sciences, University of Surrey, Guildford GU27XH, UK;*
[4]*Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy*

Chemotherapy-induced peripheral neurotoxicity (CIPN) is one of the most common dose-limiting side effects of paclitaxel (PTX) treatment. Many age-related changes have been hypothesized to underlie nerve damage. The results of these studies, however, are inconclusive and other potential biomarkers of nerve impairment need to be investigated. Twenty-four young (2-months) and 24 adult (9-months) Wistar male rats were randomized to either PTX treatment (10 mg/kg i.v. once/week for 4 weeks) or vehicle administration. Neurophysiological and behavioral tests were performed at baseline, after 4 weeks of treatment and 2-week follow-up. Intraepidermal nerve fiber density and nerve morphology/morphometry were analysed. Blood and liver samples were collected for targeted metabolomics analysis. At the end of treatment, the neurophysiological studies revealed a reduction in sensory nerve action potential amplitude ($p<0.05$) in the caudal nerve of young PTX-animals, and in both the digital and caudal nerve of adult PTX-animals ($p<0.05$). A significant decrease in the mechanical threshold was observed only in young PTX-animals ($p<0.001$), but not in adult PTX-ones. Nevertheless, both young and adult PTX-rats had reduced IENF density ($p<0.0001$), which persisted at the end of follow-up period. Targeted metabolomics analysis showed significant differences in the plasma metabolite profiles between PTX-animals and age-matched controls, with triglycerides, diglycerides, acylcarnitines, carnosine, long chain ceramides, sphingolipids, and bile acids playing a major role in the response to PTX administration. Our study identifies for the first time multiple related metabolic axes involved in PTX-induced peripheral neurotoxicity, and suggests age-related differences in CIPN manifestations and in the metabolic profile.

MALADAPTIVE PLASTICITY OF THE NEUROVASCULAR UNIT

De Luca C[1], Virtuoso A[1], Bocchetti M[2], Cirillo G[1], Scrima M[2], Papa M[1,3]

[1]*Laboratory of Neuronal Networks Morphology and System Biology, Department of Mental and Physical Health and Preventive Medicine,University of Campania "Luigi Vanvitelli", 80138, Naples, Italy;*
[2]*Molecular and Precision Oncology Lab.- Biogem Scarl, Ariano Irpino, Italy;*
[3]*SYSBIO Centre of Systems Biology ISBE-IT, Milan, Italy.*

Peripheral nerve injury (PNI) offers a unique model for studying spinal cord plasticity without directly affecting the central nervous system (CNS). The sciatic nerve lesion with sural sparing (SNI) combines motor axon damage and sensory nerve fiber loss, impacting ventral and dorsal horn neurons. The model represents a simultaneous axotomy of motor neurons in the gray matter of the spinal cord and a lesion of the peripheral processes of pseudounipolar neurons in the dorsal root ganglia (DRG). We focused on the neurovascular unit (NVU) within the lumbar spinal cord, examining early changes following SNI in rats. Our results reveal a complex interplay between the coagulation protein thrombin, its receptor PAR-1, and matrix metalloproteinase 9 (MMP9). PAR-1 is initially expressed on neurons and perivascular cells. After injury, it clusters near astrocytic endfeet, where MMP9 can cleave and activate it. MMP9 also alters the spinal extracellular matrix (ECM), particularly the basal lamina, contributing to maladaptive plasticity. Our analysis using immunohistochemistry, RNA sequencing, and RNA scope demonstrates the timely upregulation of MMP9 and its targets. Additionally, we observed changes in tight junctions and channel proteins, primarily at the protein level. Astrocytic water channel aquaporin 4 (AQP4) and gap junction protein connexin 43 (Cx43) become redistributed, and microglia/macrophages infiltrate the spinal cord. The dorsal and ventral horns exhibit distinct responses to the injury. Our findings expand our understanding of the NVU's role in spinal cord damage and highlight the importance of vascular factors in maladaptive plasticity.

IN VIVO STUDY OF CARFILZOMIB-INDUCED NEUROPATHY

Iseppon F[1], Chiorazzi A[1], Canta A[1], Alberti P[1,2], Carozzi VA[1], Pozzi E[1], Cherchi L[1], Fabbro V[1], Rodrigues-Menendez V[1] and Meregalli C[1]

[1]*Experimental Neurology Unit, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy;*
[2]*Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy.*

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of cancer treatment with chemotherapeutic agents. 20S proteasome inhibitors such as Bortezomib (BTZ) and Carfilzomib (CFZ) have been approved for treatment of multiple myeloma and other liquid tumors, also include CIPN among their side effects. To date, no effective treatment for this condition has been developed. Observations in patients treated with these drugs showed that BTZ induces a worse neuropathic phenotype when compared with ones treated with CFZ. While the strong BTZ-induced neuropathic symptoms have been replicated in a preclinical setting, there is still no preclinical animal model of CFZ-