SINS Young Meeting

Role of the Sodium–Calcium Exchanger NCX2 in Oxaliplatin-Induced Peripheral Neurotoxicity

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Oxaliplatin (OHP) is a cornerstone of colorectal cancer therapy, but its clinical use is limited by OHP-induced peripheral neurotoxicity (OIPN), which manifests as both acute and chronic syndromes. Acute OIPN is characterized by transient axonal hyperexcitability during each treatment cycle, whereas chronic OIPN features persistent axonal damage that can lead to sensory loss and neuropathic pain, substantially impairing survivors' quality of life. A mechanistic link between acute and chronic OIPN may involve the Na^+/Ca^{2+} exchanger 2 (NCX2). Increased intracellular Na^+ during the acute phase may activate reverse-mode NCX2, promoting Ca^{2+} influx and thereby contributing to later axonal damage. Here, we investigated the role of NCX2 in OIPN using an *in vitro* model.

Primary cultures of mouse dorsal root ganglion neurons were exposed to OHP to induce neurotoxicity. NCX2 expression was quantified by Western blot, and its cellular localization was assessed by immunofluorescence. To test a potential neuroprotective approach, NCX2 was selectively downregulated using siRNA. Neurite length and cell viability were measured as neuroprotection readouts.

OHP exposure altered NCX2 protein expression relative to controls. Immunofluorescence suggested a redistribution of NCX2 within sensory neurons and in satellite cells surrounding degenerating neurons. Importantly, siRNA-mediated NCX2 silencing significantly reduced OHP-induced neurotoxicity.

Overall, these data support a key contribution of NCX2 to OIPN pathogenesis and suggest that modulating NCX2 may represent a promising therapeutic strategy. More broadly, since the same pathogenic cascade was described in other peripheral neuropathies, NCX2-related mechanisms may also inform the pathogenesis and treatment of other peripheral neuropathies.