THE CRITICAL ROLE OF ZKSCAN4–TRPV1 AXIS IN THE PATHOGENESIS OF CISPLATIN-INDUCED PERIPHERAL NEUROPATHY

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Abstract - Cisplatin-induced peripheral neuropathic pain (CINP) is a major dose-limiting complication of platinum-based chemotherapy, significantly compromising patients' quality of life. Emerging evidence suggests that transcriptional dysregulation within the dorsal root ganglia (DRG) drives the pathogenesis of neuropathy. **Zinc finger protein with Krüppel-associated box (KRAB) and SCAN domains 4 (ZKSCAN4)** is a Kruppel-like zinc finger transcription factor known to function as a transcriptional repressor involved in gene silencing and cellular resilience. However, its potential role in regulating nociceptive signaling remains unexplored. In this study, we identify a novel protective role of the ZKSCAN4 axis in cisplatin-evoked pain hypersensitivity. We show that cisplatin administration significantly **downregulates** ZKSCAN4 expression in DRG neurons, which temporally coincides with the onset of mechanical allodynia. Mechanistically, we demonstrate that ZKSCAN4 functions as a transcriptional repressor of the transient receptor potential vanilloid 1 (**TRPV1**) channel; cisplatin-induced loss of ZKSCAN4 leads to the **de-repression and subsequent upregulation** of TRPV1. Importantly, **overexpression** of ZKSCAN4 effectively reverses cisplatin-induced tactile allodynia and suppresses aberrant TRPV1 levels. By characterizing the ZKSCAN4–TRPV1 pathway as a key driver of CINP, our findings provide new mechanistic insights into the transcriptional regulation of pain and establish a foundation for developing targeted therapeutic strategies.

Keywords - ZKSCAN4, TRPV1, Cisplatin-induced Neuropathic Pain, Transcriptional Repression