Novel therapeutic strategy to prevent chemotherapy-induced persistent sensory neuropathy by trpa1 blockade

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Several anticancer medicines, including bortezomib and oxaliplatin, evoke chemotherapy-induced peripheral neuropathy (CIPN), characterized by sensory symptoms (Cavaletti, 2010). No effective therapy is available to treat or prevent CIPN, most likely because its mechanisms are poorly understood. Chemotherapeutic drugs which produce CIPN, are known to increase oxidative stress and treatment with antioxidants has been shown to reduce sensory hypersensitivity in animals and to exhibit some degree of protection in patients. The transient potential receptor ankyrin 1(TRPA1) is a non-selective cation channel, expressed in a subset of C-fiber nociceptors, w here it functions as a multimodal sensor to noxious stimuli, including oxidative stress byproducts (Story, 2003; Nilius, 2007). We evaluated whether TRPA1 is a mediator of CIPN by bortezomib or oxaliplatin in a mouse model.

CIPN hypersensitivity phenotype was stably established by bortezomib and could be transiently reverted by systemic or local treatment with the TRPA1 antagonist HC-030031. A similar effect was produced by the oxidative stress scavenger α-lipoic acid. Notably, the CIPN phenotype was abolished completely in mice genetically deficient in TRPA1. Administration of bortezomib or oxaliplatin, which also elicits TRPA1-dependent hypersensitivity, produced a rapid, transient increase in plasma of carboxy-methyllysine, a by-product of oxidative stress. Short-term systemic treatment with either HC-030031 or α-lipoic acid could completely prevent hypersensitivity if administered before the cytotoxic drugs.

Our findings highlight a key role for early action of oxidative stress on TRPA1 in producing CIPN. In the future, prevention strategies for CIPN in patients could rely on early, short-term treatments with TRPA1 antagonists.

Cavaletti et al.(2010). Nat Rev Neurol 6:657-66

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