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## Abstract

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## The role of oxidative stress and the TRPA1 and TRPV4 channels in cancer-related pain syndromes

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### Abstract

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (1). Chronic pain, which may persist for years, is associated with inflammatory diseases, peripheral and central neuropathies, cancer, and idiopathic conditions, and is a distinct and debilitating condition that affects 30% of adults worldwide (2). A major challenge in pain research is to identify the pathways that sustain chronic pain (allodynia/hyperalgesia) in the peripheral and central nervous system. Identification of such pathways is essential to discover better and safer pain medicines.

The TRPA1 channel is a non-selective cation channel expressed by TRPV1-positive neurons, and a multisensor for a variety of noxious exogenous and endogenous stimuli (3), including reactive oxygen species (ROS), which plays a major role in different models of inflammatory and neuropathic pain. Among the additional TRP channels expressed in primary sensory neurons, TRPV4 has been implicated in mechanical hypersensitivity in different model of pain (4). Moreover, increasing evidence indicates that ROS sustain pain hypersensitivity in a variety of neuropathic pain models, including diabetic neuropathy (5), alcohol-related peripheral neuropathy (6), peripheral nerve injury (7), and CIPN (8).

This three-year study investigated in different pain models the ability of oxidative stress byproducts to target TRPA1 and TRPV4 on neighboring nociceptors, to initiate and maintain spontaneous pain and hypersensitivity conditions, in different models of pain.

Firstly, we investigated the role of TRP channels in the pain-like responses evoked by acute and chronic ethanol ingestion in mice. We revealed that inhibition of alcohol dehydrogenase or deletion of the TRPA1 prevented allodynia induced by alcohol ingestion. Acetaldehyde generated by alcohol dehydrogenase in both liver and Schwann cells surrounding nociceptors was required for TRPA1-induced mechanical allodynia.

Complex regional pain syndrome type I (CRPS-I) is another example of a pathological condition characterized by intractable chronic pain. In the present mouse model of CRPS-I, we revealed TRPA1 has a prominent role in initiating and sustaining mechanical and cold allodynia.

We also investigated the mechanism underlying the pain symptoms associated with CIPN. Thalidomide, a drug banned for causing birth defects in humans, has been repurposed for the treatment of several types of cancer, including multiple myeloma, myelodysplastic syndrome, and several solid cancers. Thalidomide derivatives, pomalidomide and lenalidomide, also exhibit anticancer activity in multiple myeloma patients who relapse or are refractory to other anticancer treatments. In line with the assumption that ROS contribute to CIPN, several preclinical findings have shown that mechanical and thermal hypersensitivity evoked in rodents by chemotherapeutics is attenuated by antioxidants (9). Here we revealed that peripheral TRPA1 and central TRPV4 contribute to mechanical and cold hypersensitivity elicited by thalidomide and related drugs in mice.

Finally, we evaluated the TRPs roles in cancer, as it still is a major public health problem worldwide. We revealed that in mouse models of cancer pain, macrophages were implicated in mechanical/cold hypersensitivity and spontaneous nociception and the Schwann cell TRPA1 contributed to the neuroinflammation and pain-like behavior.

Clarifying the role of TRPs and oxidative stress in different pain syndromes could have clinical importance for patients. The development of novel therapeutic strategies, involving the administration of specific antagonists that target these channels could improve pain conditions such as neuropathic, cancer related pain as well as the neuropathy derived from the treatment with anticancer drugs, thus ameliorating the

patients' quality of life.

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