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Peripheral Nerve Resident Macrophages and Schwann Cell TRPA1 in Cancer Pain

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Abstract

Pain is a common and devastating symptom ofcancer, which afflicts 70-90% of cancer patients and can diminish the quality of life more than the cancer itself. However, cancer pain remains incompletely understood and poorly managed, thus representing a major unmet medical need. A series of cytokines, chemokines, and their receptors have been proposed to contribute to signal cancer pain and although cytokines may directly or indirectly attract inflammatory and immune cells, the implication of macrophages in cancer pain remains unknown. The role of macrophages in neuropathic pain associated with nerve injury has been extensively investigated, and distinct macrophages-dependent proalgesic pathways have been identified in the central and peripheral nervous systems. Thus, neuropathic pain may be promoted by macrophages, which, recruited on demand after neural injury, rapidly invade the damaged peripheral nerves as mature and activated macrophages to promote neuroinflammation and persistent pain.

The Transient receptor potential ankyrin 1 (TRPA1), a proalgesic ion channel expressed in a subset of primary sensory neurons, is uniquely sensitive to oxidative stress byproducts. In a mouse model of neuropathic pain, TRPA1 expressed in Schwann cells was proposed to maintain mechanical allodynia elicited by oxidative stress generated by macrophages recruited at the site of nerve injury. However, the mechanism by which TRPA1 mediates mechanical allodynia associated with tumor growth is unknown. Our study aims at identifying a role for macrophages in mechanical allodynia in murine models of cancer-induced pain. We proposed that neuroinflammation and mechanical allodynia are maintained by a feed-forward mechanism which requires the continuous interaction between Schwann cell TRPA1 and expanded macrophages throughout the entire sciatic nerve trunk. Thus, macrophages, oxidative stress, and Schwann cell TRPA1 signal mechanical allodynia inmouse tumor models and may represent potential targets for the treatment of cancer pain.

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