TAKHLIQ AMIR

SUSTAINED PAIN
CHANGING OUTCOME MEASURES FOR TARGETED PAIN THERAPY

Chronic pain affects almost one-fifth of Canadians, representing around 6 million people.1 Normally, the reaction to painful stimuli involves two distinct responses. The first-line response is a reflexive withdrawal to prevent or limit injury, while the second-line response involves coping behavioural reactions, such as pressing on an injury to alleviate sustained pain.2,3 Despite being considered important evolutionary responses, the mechanism by which these signals travel between the body and the brain remains unknown.

A recent study published by Huang et al. presents an answer to this, demonstrating that separate neural pathways govern the reflexive and coping responses following an injury.4 The researchers suggest that TAC1 neurons, located in the dorsal horn of the spinal cord, mediate the sustained pain nerve-signalling pathway. By assessing pain response in TAC1-intact mice in comparison to mice with chemically-inactivated TAC1 neurons, the researchers showed that TAC1-disabled mice exhibited loss of pain-coping behaviours (e.g. paw licking), with no effect on normal withdrawal reflexes.5 In contrast, TAC1-intact mice exhibited normal prolonged paw licking following injury. It was further concluded that TRPV1 neurons, which are known to mediate the sensation of prolonged pain, connect to TAC1 neurons in the dorsal horn to relay pain signals to the brain.4

These findings are of great significance because of their clinical “bench-to-bedside” implications. Current methodologies to assess the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than the efficacy of pain-relieving compounds often measure the initial reflexive response for chronic pain assessment, rather than


OSTEOPOROSIS
A NEW MOLECULAR RECEPTOR LINKING EXERCISE AND BONE DEVELOPMENT

Osteoporosis is a disorder characterized by the age-related weakening of bone, and is commonly associated with the decrease in estrogen production in women over time.1 It is estimated that over 2 million Canadians suffer from osteoporosis.2 The decrease in bone mineral density occurs when the rate of bone resorption exceeds formation, a process largely mediated by osteoclasts, the most abundant regulatory cells found in bones.3 Since osteoclasts decrease in number over time, they play a key role in the pathogenesis of age-related osteoporosis.

Irisin is a hormone released by muscles during exercise that was discovered in 2012.4 Despite its demonstrated beneficial effects in exercise, the underlying role of irisin in the molecular mechanisms of exercise and bone development has been unclear. A team of researchers from the Dana-Farber Cancer Institute recently discovered new irisin receptors, which may represent the link between exercise and bone development.5 The newly discovered irisin receptors belong to the αv class of integrins, and enable irisin to bind to and activate osteocytes.6 Using a mouse model, the group demonstrated that injection of irisin elevated sclerostin levels, which is characteristic of bone resorption.7 Additionally, in mice that had undergone ovarioectomies to simulate osteoporosis, the genetic ablation of irisin hindered osteocytic osteolysis, thereby protecting against bone loss.8

The discovery of irisin receptors has the potential to influence future therapies for osteoporosis. Despite its role in bone resorption, some patients have shown improvements in bone density following intermittent irisin treatment.9 Future steps include investigating isoforms of irisin and its receptors as well as irisin inhibitors. Researchers are also interested in further exploring irisin’s potentially differential effects in other areas where it is highly expressed, including skeletal muscle, the heart, and the brain.10


Chimeric antigen receptor (CAR) T cells are genetically-engineered T cells that bind to specific tumour markers via their CAR receptors. This leads to CAR T cell proliferation and elimination of their target cancer cells. However, creating CAR T cells that target solid tumours is difficult because tumour tissues frequently downregulate ligands recognized by T cells. Furthermore, brain cancers, including glioblastoma, are protected by the blood-brain barrier, which prevents CAR T cells from accessing these targets.

However, a recent study conducted by Samaha et al. could circumvent this challenge. Samaha et al. noted that cancer endothelial cells overexpress a protein called activated leukocyte cell adhesion molecule (ALCAM). Binding of the T cell CD6 ligand to ALCAM allows T cells to migrate out of the blood vessel and infiltrate the brain. With this in mind, the researchers generated a highly-specific synthetic CD6 analogue with multiple binding domains for ALCAM, named homing-system CD6 (HS-CD6). This new ligand was inserted into a CAR T cell that recognizes tumour-associated antigens commonly found in glioblastoma cells. The CAR T cells were then tested in a mice model with surgically-implanted glioblastomas.

The researchers found that mice injected with the HS-CD6 CAR T cells experienced complete remission of cancer. While this finding is promising, further research is required to see if this CAR T cell therapy can also persist in an immunosuppressive microenvironment and cause minimal toxicity. Ultimately, the findings by Samaha et al. will likely contribute to a novel strategy to target solid brain tumours using CAR T cells.

Editor’s note: “A homing system targets therapeutic T cells to brain cancer” by Samaha et al. has been retracted in Nature as of 20 February, 2019 due to issues with figure presentation and underlying data.