Restraining pain

Dr Kanako Miyano, an expert on cancer and the pain it produces, shares the details of her work towards determining the relationship between certain cation channels and cancer pain.

Cancer pain can significantly impact diagnostic accuracy, patient quality of life and survival rate. Could you provide a brief overview of your research on cancer pain analgesics and discuss your overarching objectives?

We have been studying the process of pain transmission from the primary sensory neurons to the spinal cord. Primary sensory neurons have various nociceptors (sensors of pain), which are activated by a variety of noxious stimuli. When noxious stimuli activate primary sensory neurons via nociceptors, this pain information is transmitted from the primary sensory neurons to secondary sensory neurons through neurotransmitters, such as substance P (SP), a neuropeptide in the spinal cord. Among nociceptors, we focused on transient receptor potential (TRP) channels, and have elucidated mechanisms of SP release from primary sensory neurons induced by activation of TRP channels and how the released SP in the spinal cord transmits pain information to brain.

The TRP superfamily of cation channels exhibits a greater diversity in activation mechanisms than any other group of ion channels. What is their function within a chronic pain context?

Among the TRP superfamily, transient receptor potential vanilloid (TRPV)1, TRPV2, TRPV4, TRPA1, TRPM8, TRPC1, TRPC3 and TRPC6 exist in primary sensory neurons. Among these subtypes, many groups including ours have studied TRPV1 and TRPA1, and clinical trials of several compounds targeting TRPV1 or TRPA1 have been performed. The main function of TRPV1 and TRPA1 is to detect and convert environmental stimuli that are perceived as harmful into electrochemical signals that are transmitted to the central nervous system. These subtypes are activated by numerous stimuli to warn the living body of the danger as pain. TRPV1 is stimulated by capsaicin (the component of chili peppers), heat in excess of 43 °C and proton and lipid peroxidation products. TRPA1, on the other hand, is activated by allyl isothiocyanate (the pungent component of mustard oil), formaldehyde and reactive oxygen species. In addition, these subtypes are sensitised by a large number of mediators including bradykinin and prostaglandin E2.

In chronic pain the mediators produced by injury or inflammation decrease the threshold level of TRPV1 and TRPA1, so that what would normally be perceived as a mild noxious stimulus is perceived as highly noxious (hyperalgesia), and vice versa (allodynia). Thus, these channels are evidently involved in pain transmission in primary sensory neurons, and are potential targets for analgesic development.

Your research involves a functional analysis of TRPC3. Why have you chosen to study this particular gene?

Many patients with cancer (30-50 per cent of all cancer patients) will experience moderate to severe pain, which can arise at any time during the course of the disease – indicating that the mechanisms of cancer pain might be different in different stages of disease. Therefore, it might be difficult to control this complicated cancer pain by regulating only one molecule. However, TRPC3 is opened following activation of phospholipase C (PLC)-linked receptors, suggesting that many factors are able to behave as agonists of TRPC3. In cancer pain, one of the main groups of candidate agonists is the inflammatory mediators, which include bradykinin, prostaglandins and the immunoglobulin G immune complex (IgG-IC). Surprisingly, each receptor of these mediators is linked to PLC and expresses on both sensory neurons and spinal astrocytes. These facts indicate that various inflammatory mediators released from cancer cells, immune cells or injured cells activate TRPC3, expressing both sensory neurons and spinal astrocytes – and this suggests that TRPC3 plays a central role in cancer pain.

Could you briefly outline your work on the use of TRPC3 for IgG-IC-induced excitation of rat sensory neurons?

Lintao Qu et al. showed that the IgG-IC activated TRPC3 in sensory neurons through Fc-γ receptor I, a PLC-linked receptor, suggesting that IgG-IC-induced activation of TRPC3-expressing sensory neurons induces chronic pain evoked by inflammation. This report partially supports our hypothesis that TRPC3 is involved in cancer pain.

At what stage is your research? When do you foresee the translation of your work for use in a clinical setting?

Our study on TRPC3 has just started. First of all, we have to clarify the relation between TRPC3 and pain transmission using animal models or cell cultures of sensory neurons and spinal astrocytes. We then need to carefully judge whether compounds targeting TRPC3 really are safe and effective analgesics. It will be hard, and it’s a long way from completion. However, I enjoy a challenge and take great pleasure in basic science for analgesic development.
Subtracting insult from injury

A team based at the National Cancer Center Research Institute, Japan, has been studying the relationship between transient receptor potential channels and cancer pain for some time; a new study could now lead to clinical solutions.

The treatment of cancer is highly problematic for many reasons – but one of the most unpleasant problems, both in terms of the barrier it presents to treatment and the negative effect it has on the patients’ quality of life, is cancer pain. Cancer pain can be derived from a number of sources, ranging from the obvious pressure exerted by the tumour upon bones, nerves and tissue to changes brought about by tumour hormones, the immune system or even different forms of treatment. World Health Organization notes that this pain can be controlled in between 85 and 97 per cent of cases – but this level of control is not currently being achieved. In fact, reports indicate that 45 per cent of cancer pain cases are inadequately controlled.

There are many reasons for this widespread inadequate control of cancer pain, a high proportion of them tied in to the actual implementation of treatment – doctors wary of prescribing strong opioid analgesics, and patients wary of taking them for fear of addiction. The pivotal problem, however, is far simpler: the factors that drive cancer pain are still fairly poorly understood on a neurological basis. There is not even a well-accepted animal model of cancer pain to use as a firm starting point for investigation – so comfort seems far off at this point for the millions of people in the US alone who suffer from cancer pain each year.

The TRP family

The current understanding is that the biological sensation of pain begins with the nociceptors, ionic channels expressed in primary sensory neurons that are adapted for the detection of noxious, or harmful, conditions. The nociceptors are activated by various stimuli, including thermal, chemical and mechanical agitation – and upon activation they send pain signals to the central nervous system. The transient receptor potential (TRP) channels are one family of polymodal ionic channels, within which there are around 28 members. There are seven subtypes of TRP: TRPA, TRPV, TRPC, TRPM, TRPN, TRPP and TRPML. These different subtypes, and different individuals within these subtypes, can be specialised to detect different stimuli: TRPVs 1-4, TRPA1 and TRPM8, for example, are thermosensitive.

The TRP family’s role in the transmission of pain is therefore an important one, but once again, this is not a role that is fully understood. One team at the National Cancer Center Research Institute (NCCRI) in Japan has been investigating this promising family of channels for some time, with the hope of elucidating their role in pain. Dr Kanako Miyano and her team have conducted a number of studies over the last five years towards this end; although the translation of this work into new treatments for cancer pain patients may still be a little way off, the researchers have reported a number of helpful findings – and their most ambitious work is yet to come.

A promising pair

The NCCRI team has published the results of two studies so far, which have both used cultured nerve cells as a basis for investigation. The first, published in 2009, investigated the effect of paclitaxel, a chemotherapeutic agent known to often bring on adverse effects including respiratory disease, pulmonary edema and peripheral neuropathy, during and after chemotherapy. The study used a radioimmunoassay to determine the influence of this agent on the release of neurotransmitter substance P (SP) from the cultured primary sensory neurons, which play a role in transmitting nociceptive information from peripheral tissues to the brain – and its results
were very telling. According to the study, the chemotherapy drugs evoked SP release from sensory neurons – and therefore pain – by increasing intracellular Ca\(^{2+}\) concentration. The Ca\(^{2+}\) gained entry from extracellular Ca\(^{2+}\), it seems, through TRP channels.

In a follow-up study performed the following year, the team aimed to build on its results by examining whether and how the activation of neurokinin receptors could be responsible for an increase in Ca\(^{2+}\) concentration, this time in a culture of spinal astrocytes. Their findings demonstrated that SP did indeed stimulate the neurokinin receptors in spinal astrocytes, inducing Ca\(^{2+}\) release from intracellular Ca\(^{2+}\) stores, and extracellular Ca\(^{2+}\) influx through a TRP channel – this time TRPC3 specifically. Miyano and her fellow researchers might show that both cancer-induced pain and chemotherapy-induced peripheral neuropathy could be controlled using a TRPC3 blocker – a revelation that is very important to ongoing research, and also of possible clinical relevance.

**MOVING ON**

Going forward, the researchers at NCCRI will focus their attention on pursuing TRPC3, based on their studies suggesting that this specific channel may perhaps be central to cancer pain. In order to gain a deeper understanding of TRPC3’s exact role in the production of cancer pain, they have developed animal models of cancer pain – as well as carrying forward the in vitro work on their studies suggesting that this specific channel may perhaps be central to cancer pain. Miyano and her fellow researchers might show that both cancer-induced pain and chemotherapy-induced peripheral neuropathy could be controlled using a TRPC3 blocker – a revelation that is very important to ongoing research, and also of possible clinical relevance.

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**WORK IN PROGRESS**

Miyano’s group has successfully shown that both sensory neurons and non-neural cells such as glial cells are involved in the process of pain transmission. Since most analgesic drugs used in a clinical environment act only on neurons, it is not surprising that cancer pain management is as ineffective as statistics show. The current focus on TRPC3, which is expressed not only in neurons but also in astrocytes, the largest population of glial cells, could well lead to new clinical solutions – as well as constituting the basic study necessary to elucidate the mechanisms of TRPC3.

**OBJECTIVES**

- To screen for cancer pain-related mediators that activate TRPC3 using sensory neurons and spinal astrocytes; analysing functions of TRPC3 on pain transmission using sensory neurons or astrocytes, respectively
- To assess changes in expression and functions of TRPC3 in animal models of cancer pain and examine the effects of a selective TRPC3 inhibitor pyrazole-3 on cancer pain

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**KANAKO MIYANO** received her PhD degree from Hiroshima University in 2010, and performed postdoctoral studies at National Cancer Center Research Institute, Japan. She belongs to The Japanese Pharmacological Society, Japanese Cancer Association, Japanese Association for Study of Pain and Japanese Society of Neuropsychopharmacology. Miyano’s research interest is consistently focused on revealing the relation between TRP channels and pain.