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The power behind pain

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We feel pain for a reason. Either to be informed of something that is likely to hurt us more unless we turn our backs on it, or of something that has gone wrong inside us. It is a sensation that has been evolving over millions of years, from yeast to man. Pain is multiple. Understanding its vocabulary and intricate syntax can shed light on what it is, why it is and how it could be countered. Detected by receptors, the sensation of pain can be kick-started from any part of our body. The TRP receptors are a family of such receptors, activated by an array of pain stimuli. They can detect hordes of different noxious chemical compounds but also environmental sensations such as extreme heat and cold. One particular TRP receptor – TRPA1 – comes as a surprise because, unlike many of the other TRP family members, it can detect multiple sensations leading to pain, as opposed to only one.

"Hellbound", Matt Sesow

http://www.sesow.com

Over time and as a means of defense, Nature has devised the most diverse ways of hurting. Snakes spit venom. Nettles sting. Bacteria puncture. And dogs bite. However, deprived of the resources to sense pain caused by venom, or a nettle's sting or a dog's fangs, we wouldn't understand the warning that goes with it. Likewise, pain which is caused by something inside us has to be detected so that our attention can be drawn to it. To this end, pain receptors line our body's every nook and cranny, ready to send out a signal which will be relayed to our brain and translated into pain.

The Transient Receptor Potential (TRP) channels – or receptors – are pain receptors. Pain receptors are an essential part of the process which leads to the actual sensation of pain. The signal triggered off by a TRP receptor is sensed by nerve fibres which release neuropeptides that, in turn, inform the brain both of pain and inflammation. TRPA1 is one such receptor, known to be directly stimulated by the pungent components of mustard oil and garlic, which cause the familiar burning and pricking sensation we have all experienced. Besides mustard and garlic though, TRPA1 is also stimulated – though not directly – by other substances such as volatile irritants found in vehicle exhaust, tobacco products and tear gas, or components unleashed during chemotherapy treatment, or even environmental stimuli such as heat, cold. Why can TRPA1 relay so many signals of discomfort, while other TRP receptors deal with only one at a time?

Like all TRP receptors, TRPA1 is membrane-bound and most likely acts as a heterodimeric voltage-gated channel. TRPA1 has a particular secondary structure: its N-terminus is lined with a large number of ankyrin repeats which are believed to form a spring-like edifice. Most receptors have intricate pockets which are specific to a certain kind of ligand, and the slightest alteration of either the pocket or the ligand has drastic effects. Since TRPA1 can

respond to a variety of stimuli, it must have another system. Indeed, instead of presenting a pocket into which a ligand can lodge, the TRPA1 receptor forms covalently linked adducts with electrophilic compounds. The difference with other 'pocket-binding' TRP receptors is that TRPA1 ligand-binding persists for hours. The physiological response – i.e. pain in this instance – is greatly prolonged because the electrophile cannot readily dissociate from its receptor. Consequently, the receptor remains activated.

TRPA1 reacts to a variety of compounds, and does so in a variety of ways. It is directly stimulated by isothiocyanate and thiosulfinate compounds which give mustard oil and garlic their specific pungent qualities. This was discovered when mice, which didn't carry the receptor, turned out to be insensitive to both. Volatile irritants such as those found in vehicle exhaust, tear gas and tobacco smoke, as well as heat and cold stimulate TRPA1 indirectly. How? TRPA1 is part of a sensory pathway – or a number of sensory pathways – and is most likely activated or even modulated downstream of other neurotransmitter or growth-factor receptors. Funnily enough, although TRPA1 is not specific to only one component, it is surprisingly fine-tuned. As an example, the receptor is stimulated by acrolein – a compound in tear gas – yet it is insensitive to acrolein's corresponding saturated aldehyde: propanal.

Historically, mustard oil has been used extensively as a paradigm to study the mechanisms underlying inflammatory pain. Thanks to mustard oil, and a number of other substances, it has now been demonstrated that TRPA1 is capable of translating diverse signals of hostility into a singular sensation, i.e. pain. TRPA1 does seem to be on the crossroads of a number of sensory pathways. Consequently, it could prove to be an exceptional therapeutic target and may help to find ways of relieving those that suffer from chronic pain, or the secondary effects of chemotherapy and medication used in the treatment of arthritis for example. Likewise, engineering TRPA1 could help to counter the effects of noxious compounds in airways that induce not only inflammation but also chronic cough or asthma, which are a discomfort to many. Interestingly though, besides TRPA1's multiple talents, one laboratory has shown that sexual dimorphism can be an essential factor in the modulation of pain, and how it is sensed. Yet another difference between man and woman.

Cross-references to Swiss-Prot

Transient receptor potential cation channel, *Mus musculus* (Mouse) : Q8BLA8
Transient receptor potential cation channel, *Homo sapiens* (Human) : O75762

References

1. Bautista D.M., Jordt S.-E., Nikai T., Tsuruda P.R., Read A.J., Poblete J., Yamoah E.N., Basbaum A.I., Julius D.
   TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents
   Cell 124:1269-1282(2006)
   PMID: 16564016

2. Peterlin Z., Chesler A., Firestein S.
   A painful Trp can be a bonding experience
   Neuron 53:635-638(2007)
   PMID: 17329204

3. McMahon S.B., Wood J.N.
   Increasingly irritable and close to tears: TRPA1 in inflammatory pain
   Cell 124:1123-1125(2006)
   PMID: 16564004

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