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sting

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Venom has a language of its own. The recurring message is not a nice one, and usually expresses one thing: back off. Certain animals use venom – a cocktail of molecules – to ward off predators or, at the very least, to divert oncoming danger. We all know what a wasp's sting is like and many of us may have felt the sting of a jellyfish, or perhaps even the bite of a snake. It is a painful experience. To what end? The reason is twofold: one, we at once recoil from the animal that has just caused pain and two, our body is instantly told where it hurts. Concomitantly, the animal takes flight while our body attends to our wound. The feeling of pain itself is caused by the opening and closing of minute channels that riddle the membranes of our nerve cells just under our skin. This gives rise to pain signals that originate at the location of the sting, or bite, and are relayed to our brain. Understanding how pain occurs on the molecular plane helps scientists find ways of designing pain relievers. However, more often than not, pain is usually accompanied by swelling which has a protective role. So we face a conundrum: how do you relieve pain while preserving inflammation? One particular scorpion toxin, the Black Rock scorpion toxin known as the wasabi receptor toxin or WaTx, may well provide an answer.

An artwork by Asuka Hishiki

Courtesy of the artist
(drawing of a wasabi plant)

Why call a scorpion toxin a wasabi receptor toxin? One belongs to an animal, the other to a plant, neither of which bears any obvious resemblance to the other. It is because WaTx binds to an animal receptor known as Transient Receptor Potential A1, or TRPA1[1]. TRPA1s are membrane channels known to be stimulated by molecules – allyl isothiocyanates (AITCs) – that are typically found in wasabi but also in mustard, onions, and ginger for instance and bring about that disagreeable and often painful sensation inside our nose, or sometimes make us cry. This is why TRPA1s are also known as wasabi receptors.

Scorpion toxin causes pain. Fair enough. But why do natural products such as mustard and wasabi become a painful – albeit controlled – experience on our palate? The thing is, although many of us enjoy the savoury kick lent by these plants on our sensory system, AITCs probably originally evolved as a means of defence against herbivores. Besides humans, few animals would take an interest in a slice of ginger or wasabi. WaTx binds to the same receptors as AITCs – could it be that WaTx is used to ward off predators in a similar way that plant defensins are? And if we go one step further: could scorpion venom have evolved by the diversion of scorpion defensins, themselves part of a primitive immune system?

TRPA1s, or wasabi receptors, are embedded in the membranes of sensory nerve endings throughout our body and literally act as alarms against chemical irritants that can cause considerable damage to cells – like cigarette smoke and noxious gases, or irritants that are far

less harmful such as those found in wasabi, mustard or ginger. The scorpion wasabi toxin binds to wasabi receptors on their intracellular region and at a particular location that has been called the "allosteric nexus". Thanks to an unusual stretch of amino acids, WaTx can simply drift across the nerve cell membrane to reach its destination – no need for endocytosis or any other sophisticated means of transport. Such passive diffusion is particularly attractive for designing therapeutic drugs.

Structurally, WaTx looks like a rigid and compact helical hairpin which is kept stable by way of two disulphide bonds, and thus resembles many other scorpion toxins. However, its mode of action is very different: as already mentioned, unlike other toxins, WaTx is able to diffuse passively across cell membranes, and then binds to the allosteric nexus of the wasabi receptor. This is a surprising finding that prompts scientists to believe that wasabi toxins and scorpion defensins may share a common ancestor. In fact, when comparing their sequences, scientists found that only one amino-acid change was needed to go from one to the other. Such a mutation would represent a rather convenient way for scorpions to widen their hunting ground and colonise new niches as they crawled out of the water about 430 million years ago using venom to ward off predators, or indeed kill prey.

When WaTx wedges itself into TRPA1, the channel undergoes a conformational change causing it to open up for an uncharacteristically long period. Calcium levels in particular are modified; the levels inside the cells are sufficient to send pain signals to the brain, while being too low, however, to cause any swelling of the tissue. Inflammation is believed to be a response to tissue damage and used by organisms to isolate tissue which needs to be repaired. In short, WaTx hurts but does not signal to our body that part of us needs to be protected and tended to. This is precisely one of the key processes that becomes dysregulated in chronic pain.

WaTx receptors only exist in mammals and WaTx itself, in all likelihood, is purely defensive. WaTx seems an ideal candidate for developing novel therapeutic drugs such as analgesics. Not only is it able to drift through cell membranes unhindered but – like all AITCs – it binds to a very specific cytoplasmic region on wasabi receptors and, most importantly: it causes no swelling. This means that WaTx is an ideal candidate on which drug designers could build to develop pain relievers while not abolishing the essential protective role played by inflammation. Why WaTx causes no swelling of tissue is not understood. It may be strategic. Perhaps it demands less energy than the dual signal of pain and inflammation signal does. Who knows. For millennia, in human culture, scorpions have either been the embodiment of evil or indeed the incarnation of protection against evil so, in a certain way, they continue to give rise to opposing signals.

[1] Read *Protein Spotlight issue 82: The power behind pain*

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