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TRP Channels and Thermosensation

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Recent years have seen great advances in the molecular description of sensory neurobiology. Of the five popularly characterized senses (sight, hearing, taste, smell and touch), touch is perhaps the most varied and least understood. Within this modality is the ability to sense mechanical forces, chemical stimuli, and temperature, and the molecules that mediate this ability have been a long-standing mystery. Temperature sensation in particular has received relatively little attention from physiologists and yet is critical for interaction with the environment (Hensel, 1981). My group and others have recently discovered the proteins that enable sensory neurons to convey temperature information. These proteins are ion channels activated by specific changes in temperature, thus acting as the molecular thermometers of our body.

Channels play a central role in neurobiology as membrane-spanning proteins that regulate the flux of ions. Categorized according to their mechanism of gating, ion channels can be activated by signals such as specific ligands, voltage, or mechanical force. Another type of signal, temperatures above 43°C, was shown to activate the ion channel TRPV1 (VR1), a member of transient receptor potential (TRP) family of cation channels (Caterina *et al.*, 1997). These high temperatures are perceived as painful or noxious by many organisms. Interestingly, TRPV1 is also activated by capsaicin, the active ingredient of chili peppers. A second TRP, TRPV2 (VRL1) was soon found to respond to yet higher temperatures (53°C) (Caterina *et al.*, 1999). Building on these initial findings, my lab focused on identifying additional temperature-activated ion channels.

Although other members of the TRP family of channels were not known to have thermosensing roles when we started this project 3 years ago, we postulated that novel members were likely to be functionally related to TRPV1 and TRPV2. Taking advantage of the ongoing human genome project, we mined for additional TRP channels. The next step was to systematically screen these new TRPs for expression in tissues relevant for temperature sensation and to assay the activity of these channels in heterologous systems either by imaging intracellular calcium levels or by electrophysiology. As hoped, our work has led to the characterization of a novel warm-activated TRP channel, TRPV3 (33°C threshold) and two novel cold-activated TRP channels, TRPM8 (25°C threshold) and TRPA1 (ANKTM1, 17°C threshold) (Peier *et al.*, 2002a,b; Story *et al.*, 2003). TRPM8 is also the receptor for the compound menthol, providing a molecular explanation of why mint flavors are typically perceived as refreshingly cooling (McKemy *et al.*, 2002; Peier *et al.*, 2002a). Together these temperature-activated channels represent a new sub-family of TRP channels that we have dubbed thermoTRPs (Patapoutian *et al.*, 2003).

The remarkable ability of the thermoTRPs to confer temperature sensitivity to a variety of cell types suggests that they are either direct sensors of temperature or are activated via a ubiquitous temperature-activated signaling mechanism. In agreement with a role in initiating temperature sensation, most of the thermoTRPs are normally found in subsets of dorsal root ganglia (DRG) neurons. These sensory neurons convey information about the environment through specialized neurites that extend to the skin from cell bodies in the vertebral column. In fact, a single DRG neuron nerve ending marks a small spot (<1 mm in diameter) on the skin surface that often senses a narrow range of temperature stimuli. Recording directly from DRG nerve fibers has helped classify some of these neurons as hot-, warm- or cool-responsive (Patapoutian *et al.*, 2003). Still other neurons, called polymodal nociceptors, sense noxious thermal (cold and hot) and mechanical stimuli. These physiological studies strikingly correlate with results of our detailed expression analysis of the thermoTRPs in DRG neurons. We have found neurons that express only TRPV1, only TRPM8, or both TRPV1 and TRPA1(Story *et al.*, 2003). More recently, we have shown that pungent compounds including cinnamaldehyde and mustard oil activate TRPA1, reinforcing that TRPA1-expressing neurons are polymodal receptors of noxious stimuli (including noxious cold) (Bandell *et al.*, 2004). However, a surprisingly distinct expression pattern was observed for TRPV3, the warm receptor. High levels of TRPV3 are only observed in skin keratinocytes in the mouse, suggesting that skin cells might be able to 'sense' temperature and then communicate this information to DRG neurons (Peier *et al.*, 2002b). How temperature information is coded from the skin to the spinal cord and brain is not well understood, and further expression analysis of thermoTRPs could help decode this connectivity issue. Experiments with mice lacking thermoTRP expression will also be crucial for understanding the *in vivo* roles of these channels.

The need for thermosensation exists in all organisms. Therefore we have asked whether non-vertebrates also use thermoTRPs to sense temperature. We have recently shown that the *Drosophila* sequence orthologue of TRPA1 is an ion channel activated by warm temperatures, suggesting an evolutionary conserved role of TRP channels in temperature sensing (Viswanath *et al.*, 2003). This leads to the question of whether all temperature-activated ion channels are members of the TRP family. Conversely, not all TRPs are thermosensitive. However, a wide-ranging set of experiments in different species points to a recurring role of TRP channels in diverse sensory functions. These sensory TRPs act in one of two distinct ways: either as direct sensory receptors for temperature and mechanical force, or as indirect propagating signals downstream of GPCR-class sensory receptors involved in vision, taste, and olfaction (Patapoutian *et al.*, 2003). Hence another key question we are pursuing is what makes thermoTRPs temperature-sensitive while other TRPs are not?

Answering these questions requires insight into the fundamental biophysical mechanism of how temperature activates ion channels. Amino acid comparison of thermoTRPs does not immediately suggest a mechanism of temperature sensitivity. All TRPs have similar predicted secondary structure of six membrane-spanning domains with cytoplasmic termini. Otherwise, surprisingly little amino acid similarity exists between the thermoTRPs. Even TRPM8 and TRPA1, the two cold-activated TRPs, do not show significant sequence identity. Ongoing structure–function experiments, including mutagenesis and chimeric protein analysis, of the thermoTRPs will provide us with important clues about how cold or heat activates these ion channels. By identifying the proteins that likely initiate the molecular cascade leading to temperature perception, we

now have the opportunity not only to probe the basic foundation of our sense of temperature but to extend these insights into important areas of human health such as pain pathophysiology.

References

Bandell, M., Story, G.M., Hwang, S.W., Viswanath, V., Eid, S.R., Petrus, M.J., Earley, T.J. and **Patapoutian, A.** (2004) *Noxious cold ion channel TRPA1 is activated by pungent compounds and bradykinin.* Neuron, 41, 849–857.

Caterina, M.J., Schumacher, M.A., Tominaga, M., Rosen, T.A. and **Levine, J.D.** (1997) *The capsaicin receptor: a heat-activated ion channel in the pain pathway.* Nature 389, 816–824.

Caterina, M.J., Rosen, T.A., Tominaga, M., Brake, A.J. and **Julius, D.** (1999) *A capsaicin-receptor homologue with a high threshold for noxious heat.* Nature, 398, 436–441.

Hensel, H. (1981) *Thermoreception and temperature regulation.* Monogr. Physiol. Soc., 38, 1–321.

McKemy, D.D., Neuhausser, W.M. and **Julius, D.** (2002) *Identification of a cold receptor reveals a general role for TRP channels in thermosensation.* Nature, 416, 52–58.

Patapoutian, A., Peier, A.P., Story, G.M. and **Viswanath, V.** (2003) *ThermoTRPs and beyond: Mechanisms of temperature sensation.* Nat. Rev. Neurosci., 4, 529–539.

Peier, A.M., Moqrich, A., Hergarden, A.C., Reeve, A.J., Andersson, D.A., Story, G.M., Earley, T.J., Dragoni, I., McIntyre, P., Bevan, S. and **Patapoutian, A.** (2002a) *A TRP channel that senses cold stimuli and menthol.* Cell, 108, 705–715.

Peier, A.M., Reeve, A.J., Andersson, D.A., Moqrich, A., Earley, T.J., Hergarden, A.C., Story, G.M., Colley, S., Hogenesch, J.B., McIntyre, P., Bevan, S. and **Patapoutian, A.** (2002b) *A heat-sensitive TRP channel expressed in keratinocytes.* Science, 296, 2046–2049.

Story, G.M., Peier, A.M., Reeve, A.J., Eid, S.R., Mosbacher, J., Hricik, T.R., Earley, T.J., Hergarden, A.C., Andersson, D.A., Hwang, S.W., McIntyre, P., Jegla, T., Bevan, S. and **Patapoutian, A.** (2003) *ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures.* Cell, 112, 819–829.

Viswanath, V., Story, G.M., Peier, A.M., Petrus, M.J., Lee, V.L., Hwang, S.W., Patapoutian, A. and **Jegla, T.** (2003) *Opposite thermosensor in fruitfly and mouse.* Nature 423, 822–823.