



TRP channels as sensors and signal integrators of redox status changes

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Proteins are capable of sensing the redox status of cells. Cysteine residues, which react with oxidants, reductants, and electrophiles, have been increasingly recognized as the mediators of this redox sensitivity. Cation channels encoded by the *transient receptor potential (trp)* gene superfamily are characterized by a wide variety of activation triggers that act from outside and inside the cell. Recent studies have revealed that a class of TRP channels is sensitive to changes in redox status and is notably susceptible to modifications of cysteine residues, such as oxidation, electrophilic reaction, and S-nitrosylation of sulfhydryls. In this review, we focus on TRP channels, which directly sense redox status, and discuss the biological significance of cysteine modifications and the consequences of this chemical reaction for physiological responses.

Keywords: TRP channels, oxidative stress, Ca²⁺ signaling, cysteine modification, S-nitrosylation, TRPC5, TRPV1, TRPA1

INTRODUCTION

The cellular signals initiated by reactive electrophilic species, such as reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive carbonyl species (RCS) are delivered through redox chemistry. This primarily involves the post-translational modification of specific amino acid residues, especially cysteine sulfhydryls, on signaling proteins (Satoh and Lipton, 2006). According to the classical view, the reaction of cysteine sulfhydryl groups maintains protein structure through disulfide bond formation and regulates catalytic centers through metal binding (Lipton et al., 2002). However, the paradigms for function of cysteine sulfhydryl reactions have been extended by the discovery of S-nitrosylation in biological systems. The transfer of a nitric oxide (NO) group to a key cysteine sulfhydryl represents a new model of cysteine sulfhydryls acting as sensors of redox status to regulate protein functions.

The physiological significance of NO in signal transduction was established by the demonstration that NO generated by endothelial cells relaxes vascular smooth muscle through the activation of guanylate cyclase and cyclic GMP-dependent kinase (Murad, 1986). The extensive range of NO-based signaling was illustrated by the discovery of NO synthases (NOSs) with well-conserved phylogenetics and pervasive tissue distributions (Murad, 2006). In addition to the well-characterized binding of NO to the heme iron of guanylate cyclase, S-nitrosylation was suggested to be an alternative physiological NO-based protein modification (Stamler et al., 1992a,b) and this theory has been proven by the identification of more than a hundred substrates for S-nitrosylation (Stamler et al., 2001). Important examples include S-nitrosylation

of the NR2A subunit of *N*-methyl-D-aspartate (NMDA) receptors (Lipton et al., 2002), ryanodine receptors (RyR; (Eu et al., 2000), matrix metalloproteinases (MMPs; Gu et al., 2002), GAPDH (Hara et al., 2005), and protein-disulfide isomerase (PDI; Uehara et al., 2006). There is a growing awareness of S-nitrosylation as a post-translational protein modification regulated with precise temporal and spatial characteristics (Stamler et al., 2001; Barouch et al., 2002; Gow et al., 2002; Boehning and Snyder, 2003). These characteristics confer specificity to NO-derived effects, allowing S-nitrosylation to function as a prototype of mechanisms that convey redox-based cellular signals (Stamler et al., 2001).

Analogous to NO, other electrophiles can activate or inhibit specific signal transduction pathways by reacting with cysteine sulfhydryls and thus causing modification of protein structure. ROS can directly oxidize cysteine sulfhydryls *in vitro* and *in vivo* (Berlett and Stadtman, 1997). For example, H₂O₂ oxidizes sulfhydryl groups to sulfenic acid, which is rather unstable and reactive and rapidly forms stable intra- or intermolecular disulfide bonds if other adjacent sulfhydryl groups are present (Claiborne et al., 1999). Post-translational modifications include the addition of RCS on proteins, generically termed as “protein carbonylation,” with the most reactive and common form of these carbonyl groups being aldehydes. α,β -Unsaturated aldehydes, including 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ (15d-PGJ₂), 4-hydroxy-(2E)-nonenal (4-HNE), and acrolein are reactive aldehydes generated from polyunsaturated fatty acid oxidation. Because of the presence of electron-withdrawing functional groups, the double bond of these compounds serves as a site for Michael addition with the

sulfur atom of cysteine. Through the modification of key cysteine sulfhydryls, these electrophiles can mediate various biological actions including functional regulation of the I κ B kinase (IKK) β subunit, the nuclear factor (NF)- κ B p65 subunit (Rossi et al., 2000; Straus et al., 2000), kelch-like ECH-associated protein (Keap1; Eggler et al., 2005), thioredoxin (Shibata et al., 2003), and peroxisome proliferator activated receptor (PPAR) γ (Shiraki et al., 2005). Thus, highly conserved redox reactions of cysteine sulfhydryls can be elementary molecular processes in the same way as phosphorylation reactions of threonine, serine, and tyrosine residues are in cell signaling.

Studies of *transient receptor potential (trp)* proteins (TRP), which form a variety of Ca²⁺-permeable cation channels, have significantly extended our knowledge of the molecular basis of sensory biology. TRP homologs are grouped into six subfamilies [canonical (C), vanilloid (V), melastatin (M), polycystic kidney disease (P), mucolipin (ML), and ankyrin (A)] by the homology of their protein sequences (Clapham, 2003; Voets et al., 2005). Because of their distinct activation mechanisms and biophysical properties, TRP channels are highly suited to function in sensory receptor cells, either as molecular sensors for environmental or endogenous stimuli or as modulators of signal transduction cascades downstream of metabotropic receptors. In fact, TRP channels play crucial roles in many types of senses, including touch, taste, and smell in mammals (Clapham, 2003; Voets et al., 2005). Recently, it has been demonstrated that a group of TRP channels are cell sensors for changes in redox status (Hara et al., 2002; Aarts et al., 2003; Yoshida et al., 2006; Xu et al., 2008). The TRPM2 channel, the first identified ROS-sensitive TRP channel, is activated indirectly by H₂O₂ through the production of nicotinamide adenine dinucleotide and its metabolites, ADP-ribose (ADPR) and cyclic ADPR (Hara et al., 2002; Perraud et al., 2005). Accumulated evidence indicates that TRPM2 mediates several cellular responses, including the H₂O₂-activated Ca²⁺ influx that mediates cell death (Hara et al., 2002) and, in pancreatic β -cells, the Ca²⁺ or cation influx that drives insulin secretion (Togashi et al., 2006; Uchida et al., 2011). Recently, through studies using *Trpm2* knockout (KO) mice, we have demonstrated that H₂O₂-activated Ca²⁺ influx through TRPM2 induces chemokine production in monocytes, which aggravates inflammatory neutrophil infiltration (Yamamoto et al., 2008). In addition to TRPM2, certain members of the TRPC and TRPV subfamily, including TRPC5 and TRPV1, are activated directly by NO, oxidants, and other chemical agents through modification of cysteine free sulfhydryl groups (Yoshida et al., 2006). TRPC5 is also activated by reducing substances such as thioredoxin (Xu et al., 2008). More recently, TRPA1 channel activation has been shown to occur following oxidative cysteine modification by pungent compounds and inflammatory mediators (Hinman et al., 2006; Macpherson et al., 2007; Takahashi et al., 2008). Thus, TRP channels are targets of cysteine modification.

In this review, we focus on the three types of TRPs: TRPC5, TRPV1, and TRPA1 to extend our understanding of the biological significance of cysteine modifications by oxidants and electrophiles, and the physiological consequences of these chemical reactions in signal transduction pathway and in sensory neuronal responses.

TRPC5

TRPC5 was cloned from the mouse brain and functionally identified as a receptor-activated Ca²⁺-permeable cation channel linked to phospholipase C (PLC; Okada et al., 1998; Philipp et al., 1998). Although it is still controversial whether depletion of Ca²⁺ stores can activate TRPC5, a number of proteins and factors have been shown to act as direct triggers and modulators of TRPC5 channel activation. For example, binding of intracellular Ca²⁺ and calmodulin (CaM) have been implicated in TRPC5 activation and modulation (Ordaz et al., 2005; Shimizu et al., 2006; Blair et al., 2009; Gross et al., 2009), while membrane polyphosphoinositides, such as phosphatidylinositol 4,5-bisphosphate (PIP2), exert both stimulatory and inhibitory effects in regulating TRPC5 channel activity (Trebak et al., 2009). TRPC4 and TRPC1, the closest structural homologs of TRPC5, interact with the TRPC5 protein (Lockwich et al., 2000; Tang et al., 2000; Yuan et al., 2003; Obukhov and Nowycky, 2004; Goel et al., 2005; Schindl et al., 2008; Miede et al., 2010). As TRPC1 interacts with both TRPC5 and caveolin-1 (Lockwich et al., 2000; Strübing et al., 2001), it is likely that TRPC5 forms protein complexes with caveolin-1 (the importance of which will be discussed below). An array of these proteins and factors can cooperatively control the function of TRPC5 channels.

TRPC5 is potentially regulated by cysteine modifications and is activated by NO *via* cysteine S-nitrosylation (Yoshida et al., 2006). By performing labeling and functional assays with cysteine mutants, we showed that cysteine residues accessible from the cytoplasm, namely Cys553 and nearby Cys558 on the N-terminal side of the putative pore-forming region between the fifth and sixth transmembrane domains, are essential for mouse TRPC5 activation in response to NO (**Figure 1**). The corresponding cysteine sites of TRPC1, TRPC4, TRPV1, TRPV3, and TRPV4 are potential targets of nitrosylation that leads to channel activation (see also below for nitrosylation of TRPV1; **Figure 2**). NO-activated TRPC5 channels were significantly but not entirely suppressed by ascorbate, which reduces S-nitrosothiols to thiols but not disulfides. However, DTT, which reduces both S-nitrosothiols and disulfides to thiols, fully suppressed NO-activated TRPC5 channel activity. Thus, both nitrosylation and disulfide bond formation are very likely to be involved in NO-induced TRPC5 activation. In an S-nitrosylation assay (Jaffrey et al., 2001), S-nitrosylation was abolished by the mutation of Cys553 of TRPC5, whereas it was unaffected by mutation of Cys558. As proposed for the acid-base catalysis of hemoglobin nitrosylation in proteins with high NO sensitivity, basic and acidic amino acids surrounding S-nitrosylated cysteines enhance the nucleophilicity of the sulfhydryl and therefore the S-nitrosylation of this group (Hess et al., 2005). Indeed, in TRPC5, charged residues flanking Cys553 and Cys558 may confer modification susceptibility to NO. Our data may suggest that the TRPC5 channel is opened via the S-nitrosylation of Cys553 and a subsequent nucleophilic attack of nitrosylated Cys553 by the free sulfhydryl group of Cys558 to form a disulfide bond that stabilizes the open state (**Figure 1**). However, the NO sensitivity of TRPC5 channels has been disputed by several groups (Xu et al., 2008; Wong et al., 2010). It is possible that NO sensitivity of TRPC5 is dependent on culturing conditions,

own data, we can propose a plausible model to describe the role of the TRPC5 channelsome in regulating receptor-activated NO production in vascular endothelial cells (**Figure 3**). In this model, TRPC5 proteins form complexes with vasodilator receptors, G-proteins, PLC β s, and eNOS, and these complexes are anchored in caveolae by the scaffolding protein, caveolin-1. Upon vasodilator receptor stimulation, TRPC5 is activated by the PLC β cascade to induce Ca²⁺ influx, which elevates the intracellular Ca²⁺ concentration ([Ca²⁺]_i) and forms Ca²⁺-CaM. This releases eNOS from the inhibitory control of caveolin-1 and leads to an initial NO production, which activates uncomplexed TRPC5 channels. Ca²⁺ influx *via* NO-activated TRPC5 channels then induces secondary activation of eNOS to amplify the production of NO, resulting in a positive feedback cycle of receptor-activated Ca²⁺ and NO signaling. This model has been neatly summarized by Stamler and colleagues in a short review (Foster et al., 2006) based on our data (Yoshida et al., 2006).

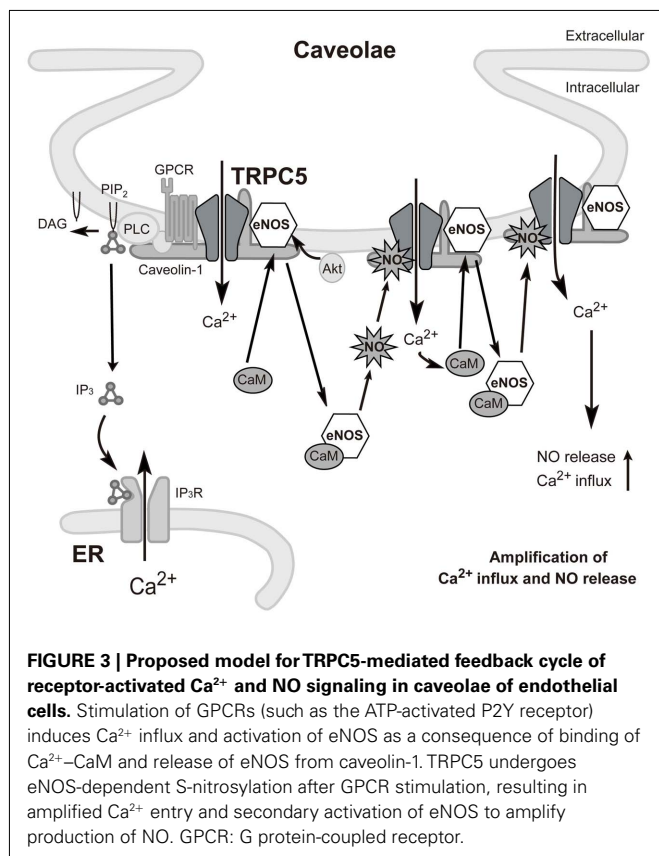
Our immunolocalization studies have revealed that TRPC5 is distributed on both the apical and basal membrane in the endothelial cell layer of vascular tissue (Mori, unpublished data). Given that vasodilator receptors are distributed at the apical luminal surface of the endothelial cell layer, an initial burst of NO produced there may diffuse across the cytoplasm and activate TRPC5 located at the basolateral membrane. This could lead to an efficient propagation of Ca²⁺ signals directed toward the basal membrane. This feedback mechanism might further contribute to global [Ca²⁺]_i elevation/oscillation and full activation of eNOS at the Golgi

(Fulton et al., 2002) of endothelial cells, leading to synchronization of neighboring smooth muscle cells during relaxation of vascular tissues. This idea is substantiated by the fact that genetic disruption of TRPC4 (the closest relative of TRPC5), which we demonstrated to be colocalized with TRPC5 in the endothelial cell membrane (Yoshida et al., 2006), impairs agonist-dependent vasorelaxation (Freichel et al., 2001). Interestingly, the importance of TRPC5 has been demonstrated in neurite extension (Greka et al., 2003). As NO signals are reported to regulate neurite extension (Zhang et al., 2005), the feedback mechanism might also be important in growth cone morphology. TRPC5 channelsomes might also be involved in the activation of eNOS by shear stress (Fulton et al., 1999; Boo et al., 2002), which is purported to proceed through a Ca²⁺-independent mechanism because membrane stretch has been reported to activate TRPC5 independently of PLC function (Gomis et al., 2008). Even where initiation of NO production is evoked independently of Ca²⁺, the secondary amplification phase might be mediated by Ca²⁺ influx via NO-activated TRPC5 channels. Thus, the positive feedback regulation of Ca²⁺ signals by NO-activated TRP channels can be involved in diverse biological systems.

TRPV1

TRPV1 is the most extensively studied and best characterized among TRP family members. TRPV1 has been implicated in a wide variety of cellular and physiological processes, including detection of noxious physical and chemical stimuli, making it a promising target for the development of analgesic drugs with ultra-specificity for the origin of the pain.

TRPV1 is a non-selective cation channel that is activated by noxious stimuli such as heat (>43°C; Caterina et al., 1997), acidic pH (Tominaga et al., 1998), and environmental irritants and endogenous algogenic substances including capsaicin (Caterina et al., 1997), camphor (Xu et al., 2005), allyl isothiocyanate (AITC) from mustard oil and wasabi (Everaerts et al., 2011), 12-hydroperoxyeicosatetraenoic acid (12-HPETE; Hwang et al., 2000; Shin et al., 2002), bradykinin (Premkumar and Ahern, 2000), and anandamide (Zygmunt et al., 1999). Although expression of TRPV1 was originally reported to be restricted to primary afferent nociceptors of the dorsal root ganglia (DRG), trigeminal ganglia, and nodose ganglia (Szallasi et al., 1995; Caterina et al., 1997; Helliwell et al., 1998; Tominaga et al., 1998; Ward et al., 2003; Brierley et al., 2005; Christianson et al., 2006), recent studies have argued for a much wider distribution, both in the central nervous system and in non-neuronal tissues (Mezey et al., 2000; Roberts et al., 2004; Tóth et al., 2005; Cristino et al., 2006; Steenland et al., 2006; Cavanaugh et al., 2011). Analysis of TRPV1-deficient mice confirmed the specificity and activation kinetics of various receptor-specific stimuli (Caterina et al., 2000; Davis et al., 2000). TRPV1 is a useful model for studying the biochemical regulation of the multimodal sensitivity of cells to stimuli. For example, the sensitivity of TRPV1 to capsaicin and noxious heat can be greatly enhanced by mild acidosis (Chuang et al., 2001; Ji et al., 2002; Amadesi et al., 2004, 2006; Sugiuar et al., 2004) and inflammatory agents that activate PLC signaling pathways (Premkumar and Ahern, 2000; Tominaga et al., 2001). Such integration of different signaling pathways allows TRPV1 to detect subthreshold stimuli,



and provides a mechanism through which tissue injury produces thermal hypersensitivity (Julius and Basbaum, 2001).

Cysteine modifications also mediate the TRPV1-activating actions of several regulatory factors (Yoshida et al., 2006). The alignment of amino acid sequences surrounding Cys553 and Cys558 of TRPC5 with counterpart sequences shows cysteines conserved on the N-terminal side of the putative pore-forming region, which is located between the fifth and sixth transmembrane domains in TRPV1. Indeed, TRPV1 channels are activated by NO by itself, while a TRPV1 mutant with substitutions at these conserved cysteines gives significantly suppressed responses to NO. NO also enhances the sensitivity of TRPV1 to H⁺ and heat, suggesting that nitrosylation-induced Ca²⁺ entry through TRPV1 is involved in heat or pain sensation. Sensitizing effects of oxidizing agents such as diamide and chloramine-T support the existence of these counterpart cysteines in TRPV1 (Susankova et al., 2006).

TRPV1 also shows sensitivity to pungent compounds from onion and garlic, such as allicin (Macpherson et al., 2005), through covalent modification of a single cysteine residue located in the N-terminal region (Salazar et al., 2008). TRPV1 activation by allicin is of physiological significance, because TRPV1 mediates part of the response to this compound in isolated DRG neurons and in an *in vivo* model. Recently, C-terminal cytoplasmic cysteine residues that sensitize TRPV1 activation upon oxidative challenge have been identified (Chuang and Lin, 2009). Robust oxidative modulation recovers the agonist sensitivity of receptors desensitized by prolonged exposure to capsaicin. Moreover, oxidative modulation operates synergistically with kinases and proton modulation. Considering that tissue damage and inflammation produce ROS, sensitization of TRPV1 under oxidative challenge is likely to play a role in nociceptor pain sensation during inflammation, infection, and tissue injury.

TRPA1

TRPA1 is the only member of the TRPA sub-branch of the TRP gene superfamily in mammals, characterized by a large number (17) of amino-terminal ankyrin repeats (Gaudet, 2008). Although TRPA1 was first cloned from a fibroblast cell line (Jaquemar et al., 1999), expression of TRPA1 is largely restricted to a subset of nociceptive C-fiber nerves, including somatosensory and vagal nerves (Story et al., 2003; Bandell et al., 2004; Jordt et al., 2004). In sensory neurons, TRPA1 was initially identified as a cold-sensitive ion channel in a small subset of cells (Story et al., 2003). Pharmacological experiments have revealed that TRPA1 is the sensory neuronal receptor for pungent compounds such as AITC (Bandell et al., 2004; Jordt et al., 2004), cinnamaldehyde from cinnamon (Bandell et al., 2004), and allicin from onion and garlic (Macpherson et al., 2005). These compounds are potentially susceptible to nucleophilic attack by the sulfhydryl groups of cysteine residues (Bautista et al., 2005; Macpherson et al., 2005). Similar to capsaicin, mustard oil activates sensory neurons, causing acute pain, thermal and mechanical hyperalgesia, and neurogenic inflammation (Jancsó et al., 1967; Bautista et al., 2006). TRPA1 is also activated by receptor stimulation (Bandell et al., 2004; Dai et al., 2007; Wang et al., 2008; Schmidt et al., 2009), cannabinoids (Jordt et al., 2004), caffeine (Nagatomo and Kubo, 2008), nicotine (Talavera et al., 2009), and heavy metals including zinc, cadmium, and copper (Hu

et al., 2009; Gu and Lin, 2010). Recent reports have demonstrated that the biophysical and pharmacological properties of TRPA1 expressed in trigeminal and vagal neurons have intriguing parallels with those of the proposed reactive airway irritant receptor (Bessac and Jordt, 2008; Taylor-Clark and Undem, 2011).

Different approaches have provided strong support for the proposal that the activation mechanism of TRPA1 by AITC and cinnamaldehyde is dependent on covalent cysteine modifications (Figure 4; Table 1). Systematic mutation of candidate acceptor sites identified three neighboring cysteines within the cytoplasmic N-terminus on human TRPA1 (Cys621, Cys641, and Cys665) whose simultaneous mutation negates the channel-activating effects of several cysteine-modifying reagents (Hinman et al., 2006). Mass spectrometry independently implicated three cysteines in mouse TRPA1 (Cys415, Cys422, and Cys622), which

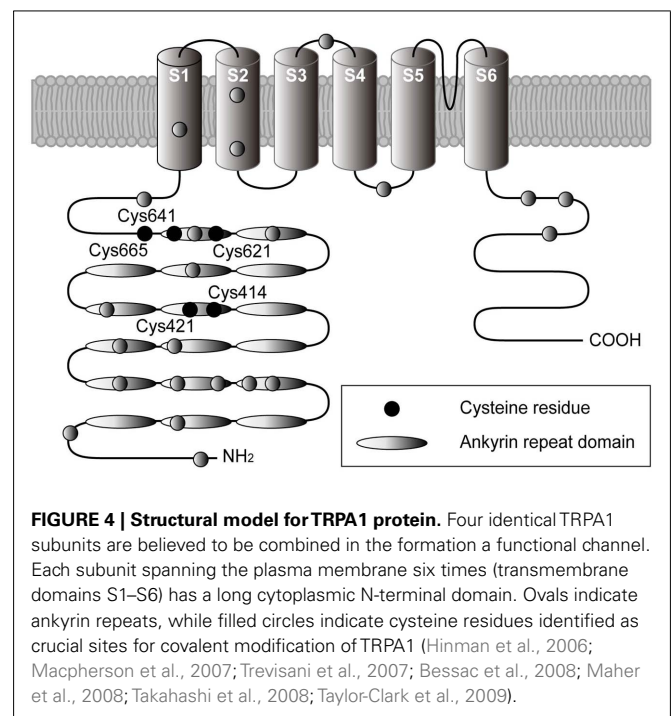


FIGURE 4 | Structural model for TRPA1 protein. Four identical TRPA1 subunits are believed to be combined in the formation a functional channel. Each subunit spanning the plasma membrane six times (transmembrane domains S1–S6) has a long cytoplasmic N-terminal domain. Ovals indicate ankyrin repeats, while filled circles indicate cysteine residues identified as crucial sites for covalent modification of TRPA1 (Hinman et al., 2006; Macpherson et al., 2007; Trevisani et al., 2007; Bessac et al., 2008; Maher et al., 2008; Takahashi et al., 2008; Taylor-Clark et al., 2009).

Table 1 | Targeted cysteine residues in human TRPA1.

Agonist	Targeted cysteine(s)	Reference
H ₂ O ₂	Cys621, Cys641, Cys665	Bessac et al. (2008)
	Cys421, Cys641, Cys665	Takahashi et al. (2008)
Hypochlorite	Cys621, Cys641, Cys665	Bessac et al. (2008)
	Cys421, Cys641, Cys665	Takahashi et al. (2008)
Nitrooleic acid	Cys621, Cys641, Cys665	Taylor-Clark et al. (2009)
15d-PGJ ₂	Cys621, Cys641, Cys665	Maher et al. (2008)
	Cys421, Cys621	Takahashi et al. (2008)
4-HNE	Cys621, Cys641, Cys665	Trevisani et al. (2007)
AITC	Cys621, Cys641, Cys665	Hinman et al. (2006)
	*Cys415, *Cys422, *Cys622	Macpherson et al. (2007)
Cinnamaldehyde	*Cys415, *Cys422, *Cys622	Macpherson et al. (2007)

*Cys415, *Cys422, and *Cys622 in mouse TRPA1.

are conserved in the human homolog (as Cys414, Cys421, and Cys621), as the target site for electrophilic agonists (Macpherson et al., 2007). Recently, we have shown that a variety of inflammatory mediators [15d-PGJ₂, NO, H₂O₂, and protons (H⁺)] activate human TRPA1 in heterologous systems and mouse TRPA1 in dissociated sensory neurons (Takahashi et al., 2008). This finding suggests that TRPA1 channels are targeted by an array of inflammatory mediators to elicit inflammatory pain in the nervous system. Functional characterization of site-directed cysteine mutants of TRPA1 in combination with labeling experiments using biotinylated 15d-PGJ₂ demonstrated that modifications of cytoplasmic N-terminal Cys421 and Cys621 are responsible for the activation of TRPA1 by 15d-PGJ₂. In TRPA1 responses to other cysteine-reactive inflammatory mediators, such as NO and H₂O₂, the extent of impairment by respective cysteine mutations differed from those in TRPA1 responses to 15d-PGJ₂. This characteristic can be attributed to a difference in the mechanisms employed by 15d-PGJ₂ and NO/H₂O₂ to achieve the modification of free sulfhydryl groups of cysteine residues in TRPA1 proteins: 15d-PGJ₂ modifies sulfhydryl groups through the Michael addition reaction, while NO and H₂O₂ modify sulfhydryl groups through the redox reaction. Interestingly, the Cys421 mutation critically impaired the TRPA1 response to H⁺ as well. Cysteine residues such as Cys421 can be deprotonated by nearby basic residues to form a thiolate anion in resting states and are protonated by acidic pH in activated states. This is a likely physiological scenario, considering that thiolate anions exert nucleophilic attack on 15d-PGJ₂, NO, and H₂O₂. According to the structural model, Cys421 is spatially located close to the basic residue His418 on the same side of an α -helix (Gaudet, 2008). Notably, TRPA1 is activated by external NH₄⁺-induced intracellular alkalization (Fujita et al., 2008) as well as acidic pH (Takahashi et al., 2008; Wang et al., 2010), suggesting that the pH dependency of TRPA1 activity has an inverted bell-shape with the minimum around physiological pH of 7.4. Interestingly, different sets of cysteine residues have been identified by independent groups (Table 1). This can be attributed to differences among mechanisms underlying modification of cysteine residues as described above for 15d-PGJ₂ and NO/H₂O₂. In RyR1, which is a redox-sensitive Ca²⁺ channel, only 12 of the 100 cysteine residues are redox-modified (“hyper-reactive” cysteines) and two of the 12 hyper-reactive cysteines are S-nitrosylated but not S-glutathionylated, whereas for a further two, the reverse applies (Aracena-Parks et al., 2006). In Keap1, which is a molecular sensor for intracellular redox changes, different cysteine residues have been reported to display different preferences for alkylating reagents (Dinkova-Kostova et al., 2002; Egger et al., 2005; Hong et al., 2005). The discrepancy may be due to the differences among the mutants employed by the groups: Hinman et al. (2006) showed data only for triple TRPA1 mutant, which carries mutations of Cys621, Cys641, and Cys665, while others used single mutants. To fully understand cysteine residues responsible for TRPA1 activation, analyses of its three dimensional structure is essential.

An array of cysteine-reactive electrophiles has been proposed as TRPA1 activators. These include a variety of RCS such as acrolein (2-propenal; Bautista et al., 2006), 4-HNE (Trevisani et al., 2007), 4-oxonon-enal (Taylor-Clark et al., 2008a), and 15d-PGJ₂ (Andersson et al., 2008; Maher et al., 2008; Takahashi et al., 2008;

Taylor-Clark et al., 2008b); ROS such as hypochlorite (Bessac et al., 2008), H₂O₂ (Andersson et al., 2008; Bessac et al., 2008; Sawada et al., 2008; Takahashi et al., 2008), and O₃ (Taylor-Clark and Undem, 2010); and RNS such as NO (Sawada et al., 2008; Takahashi et al., 2008), peroxynitrite (Sawada et al., 2008), and nitrooleic acid (Taylor-Clark et al., 2009).

Many TRPA1 stimulants activate bronchopulmonary C-fibers of vagal nerves, which innervate the airways and play a critical role in the detection of the airway microenvironment (Kubin et al., 2006). Oxidative stress and associated compounds have been shown to activate unmyelinated bronchopulmonary C-fibers, initiating action potentials in these nerves that conduct centrally to evoke unpleasant sensations such as urge to cough, dyspnea, and chest-tightness and to stimulate/modulate reflexes such as cough, bronchoconstriction, respiratory rate, and inspiratory drive (Bessac and Jordt, 2008). *In vivo* inhalation of H₂O₂ and hypochlorite given as an aerosol evokes a decrease in respiratory rate and an increase in end expiratory pause, which was abolished in *Trpa1* KO mice (Bessac et al., 2008). In addition, O₃ evokes robust action potential discharges from cinnamaldehyde-sensitive mouse bronchopulmonary C-fibers, which were reduced by approximately 80% by the generic TRP channel blocker, ruthenium red (Taylor-Clark and Undem, 2010). O₃ also causes airway nociceptor hyperexcitability (Ho and Lee, 1998; Taylor-Clark and Undem, 2010), although it is unclear if this is due to TRPA1 function. Recently, our systematic evaluation of the oxidation sensitivity of TRP cation channels using reactive disulfides with different electrophilicity reveals the capability of TRPA1 to sense O₂ in bronchopulmonary C-fibers (Takahashi et al., 2011).

The role of TRPA1 in airway afferent signaling has been studied in association with cigaret smoke and inflammation. It is well established that cigaret smoke contains nicotine and inflammation induces bradykinin, lipoxygenase products, and cyclooxygenase products, all of which can modulate airway nociceptor function independent of oxidative stress (Carr et al., 2003; Kwong and Lee, 2005; Lee et al., 2007; Taylor-Clark et al., 2008c; Talavera et al., 2009). However, both cigaret smoke (Andr e et al., 2008, 2009; Lin et al., 2010) and inflammation (Joseph et al., 2008; Kuhad and Chopra, 2009; Kamboj et al., 2010) also have the potential to modulate afferent excitability downstream of ROS production. Another important role for TRPA1 has been suggested from a mouse model of allergic asthma (Caceres et al., 2009). Allergen-induced eosinophilia, mucin production, and airway hyper-reactivity were reduced by a TRPA1 inhibitor, HC-030031 in wild-type mice by 35, 90, and 90%, respectively. These markers of allergen-induced airway inflammation were reduced in *Trpa1* KO mice. Because TRPA1 is exquisitely sensitive to oxidants, further analyses are necessary to determine whether TRPA1 activation induced by smoke and inflammation is independent of ROS.

CONCLUSIONS

Transient receptor potential channels can respond to multiple activation triggers and therefore serve as polymodal signal detectors. An important aspect of this multimodal activation of TRP channels is its role in signal integration and amplification. When a TRP channel participates in a specific signaling cascade and is activated by downstream or upstream constituents

(molecules/proteins/enzymes), in addition to the primary activation trigger immediately upstream, the TRP channel equips the cascade with positive feedback or feed-forward loops. This mechanism, which is capable of ensuring the fidelity of cellular responses and minimizing variation in their magnitude, may synchronize the responses of neighboring cells that comprise functional domains within tissues. For example, in vascular endothelial cells upon vasodilator receptor stimulation, Ca²⁺ influx *via* NO-activated TRPC5 channels can amplify production of NO by eNOS, resulting in the enhancement of NO production in nearby endothelial cells and NO-dependent relaxation of smooth muscle cells. The intercellular amplification of NO production eventually leads to vasodilation synchronized at the vascular tissue level.

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