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Chapter 9

Redox-Sensitive TRP Channels: TRPA1 and TRPM2

Makiko Kashio and Makoto Tominaga

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Abstract

The transient receptor potential (TRP) family includes cation-permeable ion channels activated by diverse stimuli ranging from chemical compounds, mechanical force and temperature. TRPA1, TRPV1, TRPC5, TRPM2, and TRPM7 are reported to be activated by reactive oxygen species (ROS). The sensitivity of TRPs to ROS is in part associated with pathogenesis caused by ROS and physiological adaptations to redox signals. The present review focuses on the well-defined ROS-sensitive TRP channels, TRPA1 and TRPM2, and summarizes recent reports regarding their activation mechanism by ROS and their relevance to pathological conditions and physiological functions in which ROS are involved.

Keywords: transient receptor potential (TRP) channel, calcium signal, pain, metabolism, body temperature

1. Introduction

Reactive oxygen species (ROS) are oxygen-derived molecules with high reactivity that are generated in diverse pathways, including by proteins of the mitochondrial respiratory chain, NADPH oxidase (NOX), dual oxidase (Duox) and cyclooxygenase (COX). Although ROS have been considered as deleterious by-products, they are generated in response to many physiological stimuli such as cytokines, hormones and mechanical force to act as signaling molecules in parallel with reactive nitrogen species (RNS), including nitrogen oxide (NO) [1]. These cellular "redox" signals are considered to play important roles in a wide range of physiological phenomena [1–3]. In the immune system in particular, H_2O_2 produced by NOX is important for removal of microorganisms and defects in redox signaling are associated with persistent infections [4]. In contrast, unregulated ROS production in pathological conditions leads to chronic inflammation and tissue damage.

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The transient receptor potential (TRP) family is a superfamily of nonselective cation channels that are homologous to the founding TRP member in *Drosophila melanogaster* that is essential for phototransduction [5]. The mammalian TRP superfamily now includes 28 members that can be grouped into six subfamilies based on amino acid sequence similarity: canonical (C), ankyrin (A), vanilloid (V), melastatin (M), polycystin (P), and mucolipin (ML). TRP channels have six transmembrane domains (S1–S6), a pore region between S5 and S6 and cytoplasmic N- and C-termini [6]. The functional TRP channel is a tetramer [7]. TRP channels exhibit a remarkable diversity in their activation mechanisms and can be activated by various ligands, both cold and hot temperatures, mechanical stimuli, or in response to signal transduction pathways. Since TRP channels can be activated by a wide range of environmental stimuli, they are considered to act as cellular "sensors." Many TRP channels, including TRPA1 and TRPM2, which are the focus of the present review, show nonselective cation (Na^+, Ca^{2+}, Mg^{2+}, K^+) permeability [5], and the activation of these channels causes membrane depolarization and, most importantly, elevated intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$) that can convert environmental information to intracellular signals.

TRPA1 is the exclusive member of the TRPA subfamily and was named for its characteristic N-terminal long 18 ankyrin repeat domain (ARD), a motif that is thought to mediate protein–protein interactions [8]. TRPA1 is abundantly expressed in nociceptive primary afferent sensory neurons that detect nociceptive stimuli. TRPA1 is expressed in sensory neurons of dorsal root ganglia (DRG), trigeminal ganglia (TG), and nodose ganglia, as well as many other organs and tissues, including the brain, heart, small intestine, lung, skeletal muscle, and pancreas [9]. Because TRPA1 has broad sensitivity to reactive compounds, it can detect a wide range of hazardous compounds (see below). TRPA1 function is modulated by endogenous intracellular factors such as membrane lipids and Ca^{2+}, which has bimodal effects on TRPA1 function. EF-hand-like domains in the N-terminus between the 11th and 12th ankyrin repeat of TRPA1 are reported to form a Ca^{2+}-binding site responsible for Ca^{2+}-dependent mTRPA1 activation [10, 11]. TRPA1 desensitization can also depend on Ca^{2+} [12].

TRPM2 is a member of the TRPM subfamily that functions as a nonselective cation channel. TRPM2 is known as a "channezyme," that is, an ion channel that possesses an enzymatic region, based on its C-terminal Nudix domain that is homologous to the NUDT9 adenosine diphosphoribose (ADPR) pyrophosphatase, an enzyme that converts ADPR to adenosine monophosphate and ribose 5-phosphate [13]. However, the TRPM2 Nudix domain lacks ADPR hydrolase activity and its binding to ADPR is sufficient for channel gating [14, 15]. Adenosine diphosphoribose (ADPR), cyclic ADPR and pyridine dinucleotides, including nicotinamide-adenine-dinucleotide (NAD), nicotinic acid-adenine dinucleotide (NAAD) and NAAD-2′-phosphate (NAADP), have been reported as endogenous agonists for TRPM2. However, TRPM2 activation by pyridine dinucleotides was later shown to have been caused by ADPR contamination, and thereby, pyridine dinucleotides are likely not TRPM2 agonists [16]. TRPM2 is also activated by reactive oxygen species [17] and is therefore considered to be redox-sensitive. TRPM2 is regarded as a "metabolic sensor" because its activity is regulated by cellular and systemic metabolic states such as redox signaling, glucose levels and body temperature [18–20]. As with TRPA1, Ca^{2+} plays crucial roles in TRPM2 activation

[21], and Ca^{2+} binding to the intracellular pore cavity is necessary for channel activation [22]. Meanwhile, intracellular H^+ ions reportedly inhibit TRPM2 function [23].

TRPM2 is expressed in the plasma membrane of many cell types such as neurons and microglial cells in the brain, vascular endothelial cells, pancreatic β-cells and immunocytes, as well as tissues in the spleen and liver [24]. Several reports showed that TRPM2 also functions in the lysosomal membrane [25, 26].

Despite fluctuating environmental temperatures, endothermic species such as mammals and birds can maintain a constant body temperature through the activity of peripheral thermal sensors in sensory and autonomic neurons and by thermosensitive structures within the preoptic area (POA), anterior hypothalamus, brain stem, spinal cord and possibly other places that regulate body temperatures through autonomic and behavioral mechanisms [27]. TRPM2 was recently shown to be expressed in warmth-sensitive neurons of the POA and in peripheral sensory and autonomic neurons, suggesting that TRPM2 is involved in regulating body temperature [28, 29].

2. Activation mechanism of TRPA1 by reactive oxygen/nitrogen species and diverse chemical compounds

TRPA1 is expressed in primary sensory neurons and mediates noxious pain sensations evoked by a wide range of reactive compounds. Electrophilic TRPA1 activators have environmental, dietary and endogenous origins and include acrolein (air pollutant), allyl isothiocyanate (in mustard), allicin and diallyl disulfide (in garlic), cinnamaldehyde (in cinnamon) and the proalgesic lipid peroxidation products 4-hydroxynonenal (4-HNE) and 15-deoxy-Δ12,14-prostaglandin J_2 (15d-PGJ_2) (**Figure 1A**) [30–33]. These compounds are collectively referred to as reactive carbonyl species (RCS). Many have highly reactive electrophilic carbon moieties such as an αβ-unsaturated carbonyl group. These moieties react with cysteine thiol groups in TRPA1, including those located between the N-terminal ARD and S1 (Cys621, Cys641, Cys665) of human TRPA1, which results in covalent modification by S-alkylation through a Michael addition that in turn activates TRPA1 (**Figure 1B**) [31]. In mouse, TRPA1, Cys415 and Cys422 in ARD and Cys622 between ARD and S1 are required for activation by reactive compounds [33]. In addition to cysteine residues, lysine (Lys708 in human TRPA1) is also reportedly involved in TRPA1 activation by reactive electrophilic species, although the contribution of this amino acid seems to be limited to the action of AITC [31].

TRPA1 is also activated by reactive oxygen/nitrogen species (ROS/RNS) and thus is regarded to be "redox-sensitive". TRPA1 is activated by many kinds of ROS and RNS, including hydrogen peroxide (H_2O_2), hydroxyl radical (OH·), hypochlorite (OCl^-), nitric oxide (NO) and peroxynitrite ($ONOO^-$) [32, 34, 35] (**Figure 1A**). Oxidative stress endogenously generates lipid peroxidation products such as 4-NHE and 15d-PGJ_2, described above as RCS. However, ROS can activate TRPA1 independently of these peroxidation products, as evidenced by the finding that H_2O_2-induced TRPA1 activation is reversed by the application of dithiothreitol

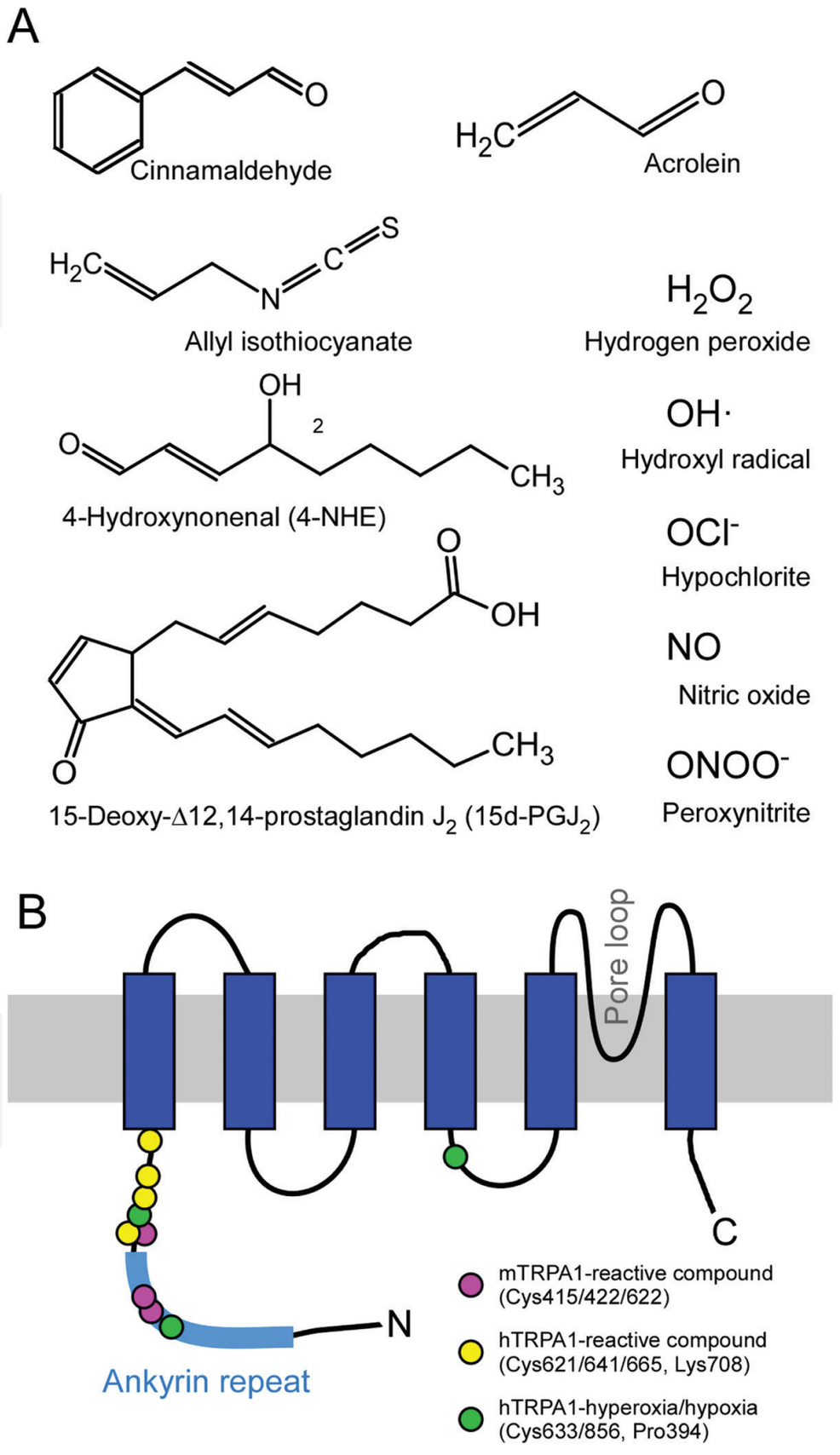


Figure 1. Chemical structure of TRPA1-activating reactive compounds (A) and reported target amino acid residues in TRPA1 (B).

(DTT), which reverses cysteine disulfide formation, nitrosylation and cysteine oxidation, but not Michael addition, without affecting the action of 4-NHE and 15d-PGJ_2 [32, 36]. This result suggests that ROS induce cysteine oxidation and disulfide formation between proximal cysteine residues in TRPA1.

TRPA1 activation by RNS is considered to be mediated by S-nitrosylation of cysteine residues, since TRPA1 activation by the NO donor SNAP was reversed by the application of DTT as described above [36]. Functional characterization of site-directed cysteine mutants of mouse TRPA1 demonstrated that modification of several cysteine residues (Cys621, Cys641, Cys665) involved in RCS activation mediates the action of ROS and RNS [34, 35]. However, mutation of cysteine and lysine residues could also affect channel activation by nonelectrophilic agonists, which would complicate the identification of amino acids responsible for covalent modification of TRPA1 [35]. TRPA1 activation by these reactive compounds leads to pain sensation that would diminish the likelihood of deleterious damages arising from adducts formed by these compounds and DNA or proteins that are associated with carcinogenesis and toxicity [37].

3. Activation mechanism of TRPM2 by redox signaling

TRPM2 channels are activated by H_2O_2 [17], and this activation could be enhanced by pretreatment with Fe^{2+} to promote formation of hydroxyl radicals generated by the Fenton reaction that are also thought to have an important role in TRPM2 activation [38]. Indirect TRPM2 activation through the production of intracellular ADPR and direct action independent of ADPR production have also been reported (**Figure 2A**). One ADPR production pathway involves nuclear poly(ADPR) polymerases (PARPs) and poly(ADPR) glycohydrolases (PARGs). PARP is activated by DNA damage upon oxidative stress and has DNA repair functions [39]. Meanwhile, PARG hydrolyzes poly-ADPR chains to generate free ADPR. The finding that treatment of cells with a PARP inhibitor decreased H_2O_2-mediated TRPM2 activation supports a role for ADPR in activation of this channel [40]. Another possible source of ADPR is mitochondria, where oxidative stress could induce the production of free ADPR [41]. Indeed, reduced mitochondrial ADPR concentrations suppressed H_2O_2-mediated TRPM2 currents [42]. ADPR can also be produced by plasma membrane/intracellular organelle CD38, which has implications for immunocyte function [43, 44]. However, the mechanism by which extracellular ADPR generated by the CD38 ecto-enzyme enters the cells is unclear [45]. In contrast, an ADPR-independent TRPM2 activation pathway may also exist based on the finding that a TRPM2 variant lacking the Nudix domain that contains the ADPR-binding domain still responded to H_2O_2 [46]. In addition, our recent results showed that H_2O_2 clearly enhanced heat-evoked responses of TRPM2 in inside-out single channel recordings in which intracellular components were completely absent (**Figure 2B**) [19]. This action was accompanied by a reduction in the temperature threshold for TRPM2 heat activation (**Figure 2C**) and was mimicked by an oxidant that reacts with methionine residues. Taken together, these results suggest that ADPR-independent actions could also be involved in TRPM2 activation; however, because H_2O_2-evoked reduction in the temperature threshold for TRPM2 activation was affected by a PARP inhibitor, there could be both direct and indirect actions in H_2O_2-mediated effects.

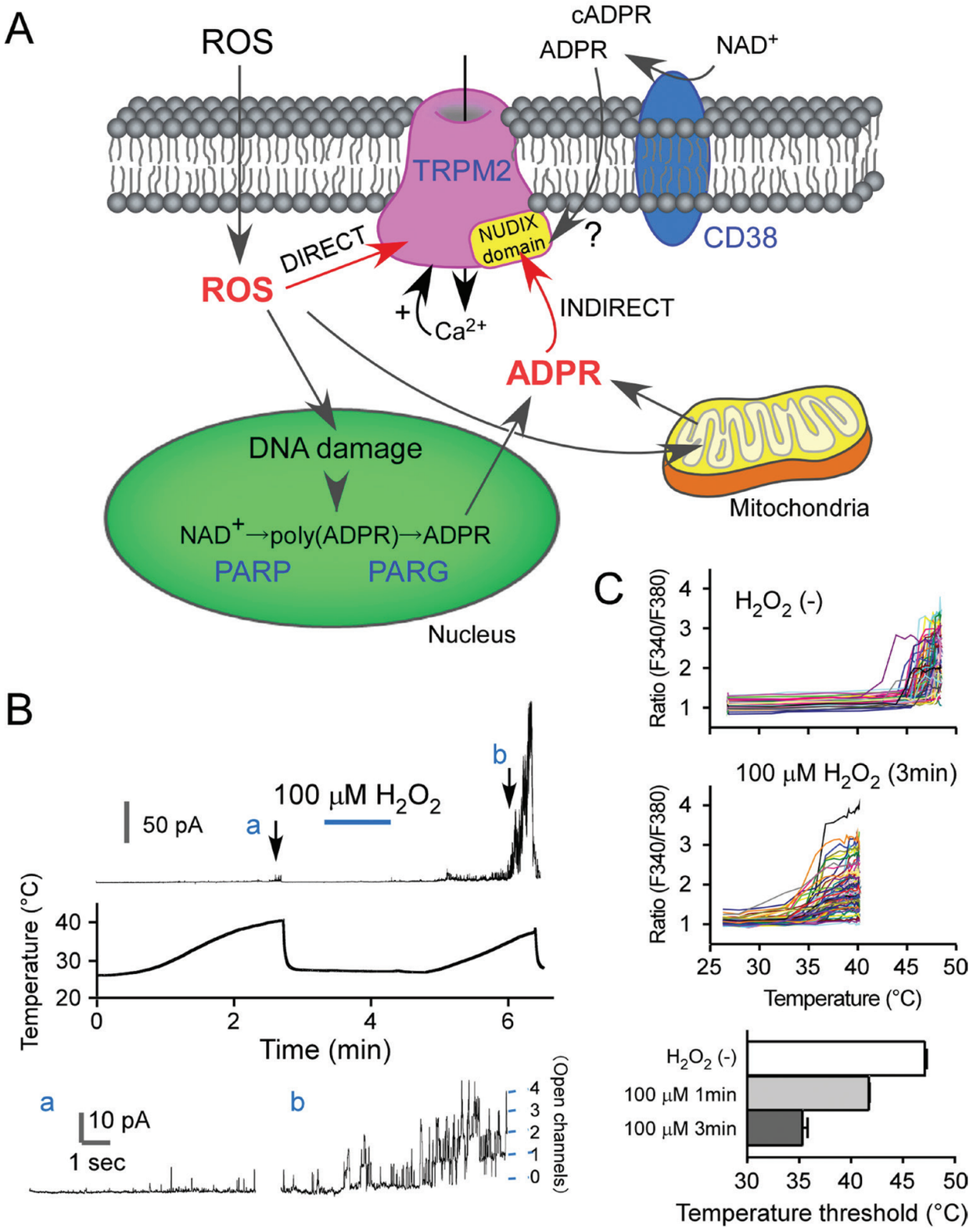


Figure 2. (A) Scheme showing the activation cascade of TRPM2 by reactive oxygen species (ROS). (B) H_2O_2-enhanced heat-evoked single channel opening observed in inside-out single channel recordings. (a,b) Magnified traces at the time points indicated in the upper column. (C) H_2O_2-treatment lowered the temperature threshold for TRPM2 activation. The temperature-fura2 ratio relationship is plotted for H_2O_2-untreated and H_2O_2-treated (100 μM, 3 min) cells. Average temperature thresholds for each group (Mean ± SEM) are shown.

4. Pathological and physiological relevance of redox signal-regulated TRPA1 activation

TRPA1 is abundantly expressed in a portion of primary sensory neurons and mediates noxious pain sensation evoked by ROS to avoid deleterious DNA damage. In an inflammatory milieu, phagocytes release large amounts of ROS that promote the production of endogenous lipid compounds, including the RCS 4-HNE and 15d-PGJ_2. These compounds activate TRPA1 to cause inflammatory pain [36, 47].

TRPA1 is readily modified by electrophilic compounds. An analysis of the redox potentials of reactive disulfides revealed that TRPA1 has the lowest redox potential threshold among TRPA1, TRPV1, TRPV2, TRPV3, TRPV4, and TRPC5, indicating its high sensitivity to electrophilic compounds [48]. Thus, TRPA1 could act as a hyperoxia sensor in vagal and sensory nerves (**Figure 3**). Heterologously expressed TRPA1 was activated through covalent modification of cysteines at high oxygen conditions in excess of atmospheric oxygen concentration (20% O_2) (hyperoxia), and the activation was diminished by point mutation of TRPA1 cysteine residues (Cys633Ser and Cys856Ser) (**Figure 1B**). In addition, hypoxic conditions also activated TRPA1, which could be suppressed by overexpression of recombinant prolyl hydroxylase (PHD). The oxygen-sensitive PHD catalyzes proline hydroxylation of TRPA1 under normoxic conditions that in turn inhibits channel function. A PHD inhibitor activated TRPA1 even under normoxic conditions, suggesting the involvement of proline hydroxylation in TRPA1 activation. Under hypoxic conditions, basal enzymatic activity of PHD is inhibited and TRPA1 is activated upon relief of proline hydroxylation-mediated inhibition. A proline residue located in the TRPA1 N-terminus (Pro394) is suggested to be involved in proline hydroxylation-mediated TRPA1 inhibition (**Figure 1B**). Indeed, vagal nerves isolated from wild type, but not TRPA1-knockout (KO) mice, showed $[Ca^{2+}]_i$ increases respond to both hyperoxic and hypoxic conditions. These data suggest that TRPA1 could function as an O_2 sensor to control respiratory, cardiac and vascular functions through cysteine oxidation by ROS and proline modification by the oxygen-sensitive enzyme PHD. Proline hydroxylation of TRPA1 is also considered to participate in cold sensitivity of this channel, although this possibility remains a subject of debate (**Figure 3**). Temperature sensitivity of mammalian TRPA1 varies among species [49] in

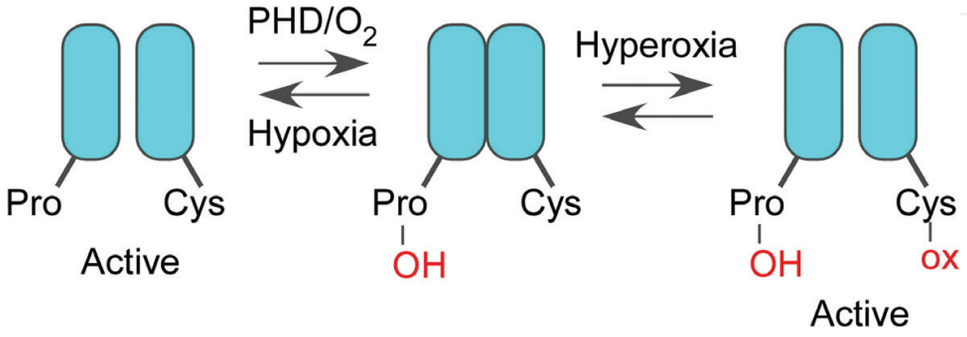


Figure 3. TRPA1 regulation by Cys-oxidation (Cys-Ox) and Pro-hydroxylation at different oxygen concentrations. PHD, proline hydroxylase.

that human TRPA1 and monkey TRPA1 are not activated by cold stimulus whereas rat TRPA1 and mouse TRPA1 are. Mutation of Gly878 in S5 of rat TRPA1 to Val that is present in human TRPA1 abolished cold sensitivity. A proline hydroxylation-deficient mutant of human TRPA1 (Pro394Ala) was activated by cold stimulation in the presence of low concentrations of H_2O_2 (0.1 μM), but wild-type TRPA1 showed no activation [50]. PHD inhibitors could result in activation of wild-type TRPA1 by cold temperature, which is attenuated by mitochondrial ROS scavenging. H_2O_2-evoked responses were significantly larger for Pro394Ala TRPA1 than for wild type, and a PHD inhibitor increased the response of wild-type TRPA1. In contrast, mouse wild-type TRPA1 was activated by cold temperature and effects of the PHD inhibitor and ROS scavengers were also observed in a mouse TRPA1 clone, confirming that the inhibitory effect of proline hydroxylation was conserved between human and mouse. Several chemotherapeutic agents can cause cold allodynia [51–53]. For instance, the drug oxaliplatin potentiates H_2O_2-induced responses in mouse DRG neurons possibly by inhibiting PHD [50].

TRPA1 is also reported to play a physiological role in artery vasodilation, although its activity varies among different types of vascular beds. In cerebral arteries, TRPA1 expressed in the endothelium mediates "endothelium-dependent" vasodilation. ROS such as superoxide anions (O_2^-) and hydrogen peroxide (H_2O_2) are known to cause vasodilation, leading to increases in cerebral microcirculation [54]. TRPA1 mRNA expression was observed in the endothelium of cerebral arteries, but not in peripheral vascular beds in renal, coronary and mesenteric arteries [55]. TRPA1 protein in the endothelium of cerebral arteries preferentially colocalizes with NOX2, a ROS-generating enzyme, in fenestration of internal elastic lamina where plasma membranes of endothelium and smooth muscle cell are in close contact. ROS generated by NADPH-induced NOX activity led to cerebral artery vasodilation following TRPA1 activation. This vasodilation could be abolished in a variety of ways, including by a NOX inhibitor, catalase-mediated degradation of H_2O_2, deferoxamine, which inhibits the Fenton reaction that generates hydroxyl radical (OH^-), the TRPA1 inhibitor HC-030031 and TRAM34, a blocker of the intermediate conductance Ca^{2+}-sensitive K channel (IK). Moreover, vasodilation could be mimicked by application of 4-hydroxy-nonenal (4-HNE), a product of lipid peroxidation. These results suggest that ROS-derived lipid peroxidation products activate TRPA1, leading to cytosolic Ca^{2+} elevation, which in turn activates intermediate conductance Ca^{2+}-sensitive K channels (IK) and membrane hyperpolarization in the endothelium. This change in membrane potential is propagated through gap junctions to smooth muscle cells to promote additional vasodilation. On the other hand, in peripheral arteries, TRPA1 expressed in primary sensory neurons is reportedly involved in "neurogenic" vasodilation. TRPA1 expressed in sensory neurons likely mediates vasodilation in peripheral arteries because TRPA1 is not expressed in the endothelium of peripheral arteries [56]. Topical application of cinnamaldehyde, a TRPA1 agonist, onto mouse ears caused vasodilation in wild-type mice, but not in TRPA1KO mice. TRPA1 agonist-induced vasodilation could be attenuated by a CGRP antagonist, a nonselective NOS or a neuronal NOS (nNOS) inhibitor, suggesting the possible involvement of CGRP and NO release from sensory neurons. In addition, TRPA1 agonist-induced vasodilation is mediated by formation of superoxide and peroxynitrite.

Taken together, TRPA1 expressed in the endothelium of central arteries is involved in endothelial-dependent vasodilation, whereas TRPA1 expressed in vagal and primary sensory neurons functions in neurogenic vasodilation in peripheral arteries.

5. Pathological and physiological relevance of redox signal-regulated TRPM2 activation

TRPM2 activation induced by H_2O_2 promotes cell death due to sustained elevation of intracellular Ca^{2+} [17] and also increases inflammation and tissue injury [18]. Therefore, numerous reports have shown the implications of TRPM2 activity in oxidative stress-induced cell death of many kinds of tissues and cells [57]. Endogenous and exogenous agents that promote ROS production such as TNFα, β-amyloid, and neurotoxin MPTP also cause neurotoxicity in a TRPM2-dependent manner [17, 58–61]. In addition, ischemia/reperfusion (I/R) injury is a major pathological situation involving unregulated ROS production in stroke, brain trauma, cardiac arrest and other disorders and diseases. Ischemia is the restriction of blood flow that diminishes oxygen (hypoxia/anoxia) and glucose supplies to tissues. When blood supply is restored to the affected tissues, secondary effects associated with I/R injury can occur wherein inflammatory agents and ROS that can cause tissue damage are produced. ROS-evoked TRPM2 activity was reported to aggravate tissue damage in the presence of I/R injury [62–64], and this situation can be explained in part by increased neutrophil migration toward affected tissues [63, 65].

On the other hand, more recent reports suggest that TRPM2 could exert protective roles in I/R injury. One group reported that TRPM2 channels are expressed in the sarcolemma and transverse tubules of adult cardiac myocytes [66, 67]. They also showed that TRPM2KO heart is vulnerable to I/R injury and I/R-induced prolongation of action potential duration was enhanced in TRPM2KO myocytes compared with wild type [67]. Proteomic analysis of I/R-affected ventricles from wild-type and TRPM2KO mice revealed that, relative to wild-type heart, mitochondrial respiratory complex dysfunction in TRPM2KO heart is more severe and is associated with altered expression levels of proteins localized in the mitochondrial inner membrane [68]. Under I/R conditions, TRPM2KO myocyte mitochondria showed lower mitochondrial membrane potential, Ca^{2+} uniporter activity, ATP levels and oxygen consumption as well as higher ROS levels compared to those seen for wild type. These data suggest that Ca^{2+} supplied by TRPM2 activity can have a protective role by ameliorating mitochondrial dysfunction and diminishing mitochondrial ROS levels in I/R situations. Similar results were recapitulated in intact and TRPM2-depleted SH-SY5Y neuroblastoma cells treated with the ROS-generating chemotherapeutic agent doxorubicin [69]. Interestingly, these diminished parameters of mitochondrial function in TRPM2KO myocytes were also seen under normoxic conditions [68]. Considering these results, TRPM2 may contribute to the maintenance of basal mitochondrial bioenergetics by supplying Ca^{2+}, which has numerous functions in mitochondrial metabolism [70].

TRPM2 also has roles in inflammation and infection as evidenced by its expression in immunocytes (**Table 1**). In inflammatory situations, ROS are produced and ROS-evoked TRPM2 activity can aggravate inflammation. At sites of inflammation, phagocytes such as neutrophils and macrophages digest deleterious agents and increase oxygen consumption that enhances NOX-mediated production of ROS, phagocytized agents can then be cleared by ROS. TRPM2 is widely expressed in leukocytes, including lymphocytes, neutrophils, monocytes/macrophages, dendritic cells, microglia and mast cells [19, 25, 71–75]. TRPM2 activation by ROS is

In vivo **model**	**The effects of TRPM2 down regulation**
DSS-induced colitis [73]	CXCL2↓, neutrophil infiltration↓ inflammation↓
Listeria monocytogenes [85]	Survival rate↓, CXCL2→, neutrophil infiltration→, $iNOS^+$ monocyte↓
CLP-induced sepsis [87]	Survival rate↓, inflammation↑, IL-6↑, HMGB↑, bacterial clearance↓
PA i.t., CLP [84]	Survival rate↓, bacterial clearance↓
LPS i.p. [89]	Survival rate↓, inflammation↑, CXCL2↑, TNFα↑, IL-6↑, neutrophil infiltration↑, ROS production↑

In vitro **model**	**Stimulus**	**The effect of TRPM2 down regulation**
U937 monocyte [73]	H_2O_2	CXCL8 (human homolog of CXCL2)↓
Peritoneal macrophage [19]	Zymosan	CXCL2↓, GCSF↓, IL-1α↓, IL-1β↓[#], TNFα→, Temp-phagocytosis↓
BMDM [76]	Liposome	Inflammasome activation↓, IL-1β↓, TNFα→, ROS production→
U937 monocyte [82]	High glucose	Inflammasome activation↓, NOX activation↓, IL-1β↓
BMDM [84]	PA, SA	Phagosomal acidification↓, Bacterial clearance↓

Table 1. Reports showing the implication of TRPM2 in immune reactivities using *in vivo* and *in vitro* models.

reported to worsen inflammation by elevating cytokine release. Indeed, TRPM2 activation in mouse monocytes elevates H_2O_2-induced release of the neutrophil-attracting chemokine macrophage inflammatory protein-2 (CXCL2) through activation of the Ca^{2+}-dependent tyrosine kinase (Pyk2) and nuclear factor κB (NFκB), and this elevation was attenuated in TRPM2KO monocytes [73]. Supporting these *in vitro* experiments, wild-type mice showed elevated CXCL2 levels and neutrophil infiltration in inflamed colon tissues with ulcerative colitis in a dextran sulfate sodium (DSS)-induced experimental colitis model. These conditions are suppressed in TRPM2KO mice, suggesting that TRPM2 activation in monocytes increased chemokine release and neutrophil migration followed by aggravation of inflammation. In our experiments, TRPM2 activity elevated release of the cytokines granulocyte colony stimulating factor (G-CSF), interleukin-1α (IL-1α), and CXCL2 from macrophages [19]. TRPM2-mediated exacerbation of inflammation also explains pathological conditions associated with chronic pain. TRPM2KO mice showed impaired pain responses in inflammatory pain induced by intraplantar injection of formalin or carrageenan in mice, and neuropathic pain models induced by partial sciatic nerve ligation or spinal nerve transaction [76]. TRPM2 activity in macrophages and microglia is suggested to aggravate chronic pain through CXCL2 release and neutrophil infiltration toward inflamed tissues.

Nod-like receptor family pyrin domain containing-3 (NLRP3) inflammasomes are activated by several conditions of cellular stress, including microbial products, particulate substances,

elevated plasma glucose levels that accompany metabolic disorders, intracellular [K^+] reduction and $[Ca^{2+}]_i$ increase [77, 78]. NLRP3 inflammasome is a complex of NLRP3, apoptosis-associated speck-like protein (ASC) and caspase-1 to activate caspase-1 that in turn promotes release of pro-inflammatory cytokines, IL-1β and IL-18. TRPM2 is reported to be involved in the inflammasome activation in macrophages/monocytes. Charged liposomes evoke ROS production, caspase-1 activation and IL-1β release from bone-marrow-derived macrophages (BMDM) [79]. Caspase-1 activation and IL-1β release evoked by liposomes are attenuated by TRPM2 deficiency, although mitochondrial ROS production is comparable to that of wild type. Thioredoxin-interacting protein (TXNIP) is known to bind to NLRP3 and participate in ROS-dependent inflammasome activation [80]. TXNIP expression is up-regulated by high glucose and is involved in ROS production induced by high glucose [81]. Treatment of U937 monocytes with high levels of glucose induced TRPM2 up-regulation, ROS production, caspase-1 activation and IL-1β release, which can be attenuated by TRPM2-siRNA or TRPM2 inhibitors [82]. TXNIP up-regulation by high glucose is also inhibited by TRPM2-siRNA. Upon activation of NOX, p47phox, a cytosolic subunit of NOX, translocates to the plasma membrane. Under high glucose conditions, p47phox translocation is increased as is its co-localization with TRPM2. In addition, co-localization of TXNIP and NLRP3 is enhanced by high glucose conditions, which could also be suppressed by TRPM2-siRNA. These data suggest that Ca^{2+} influx through TRPM2 can contribute to high glucose-induced ROS production as well as inflammasome activation and amplification of TRPM2 activation to further exacerbate oxidative stress in diseases such as type 2 diabetes.

An important role of macrophages, phagocytosis, is regulated by TRPM2 activity. As mentioned above, macrophages phagocytose deleterious agents such as exogenous pathogens and digest them in phagosomes by producing ROS levels that are toxic to the pathogens. This phagocytosis function is known to be enhanced by temperatures that are associated with fever [83]. Phagocytosis induced by toll-like receptor 2 agonist was enhanced by temperature elevation to febrile range in wild-type macrophages which can detect slight temperature change through TRPM2 activity in the presence of low concentration of ROS [19]. On the other hand, TRPM2KO macrophages showed no such temperature-dependent elevation of phagocytosis, suggesting that ROS generated in phagosomes increases TRPM2 sensitivity to body temperature and that TRPM2 activation by temperature increases phagocytosis. Because TRPM2 is highly localized in phagosomal membranes [84], functional cooperation between TRPM2 and NOX is suggested to increase phagocytosis. As many reports have shown roles for TRPM2 in innate immunity, the physiological roles of TRPM2 have been studied in microbial infection models. In a *Listeria monocytogenes* (Lm) infection model, TRPM2KO mice show lower serum IL-12 and IFNγ levels and a higher mortality rate than wild-type mice; these conditions can be reversed by the application of IFNγ [85]. In contrast to the DSS-induced experimental colitis model [73], Lm-infected TRPM2KO mice have CXCL2 expression and neutrophil infiltration in the spleen that is comparable to wild-type mice. Given that the ratio of activated monocyte ($iNOS^+$) is decreased and IL-12 release is unchanged in an *in vitro* cytokine release assay using BMDMs from Lm-infected TRPM2KO, TRPM2 activation is suggested to have important roles in reciprocal activation among macrophages, natural killer cells, and $CD8^+$ T cells mediated by IL-12 and IFNγ during the early phase of Lm infection [86]. TRPM2 deficiency is also

reported to increase the mortality rate in a cecal ligation and puncture (CLP)-induced polymicrobial sepsis model [87]. Moreover, TRPM2KO mice show increased bacterial burden and enhanced inflammation and injury in tissues. TRPM2-deficient BMDM show lower bacterial killing than that of wild type without noticeable effects on phagocytosis. Lipopolysaccharide (LPS) treatment of BMDM from wild-type and TRPM2KO mice revealed that heme oxygenase-1 (HO-1) induction observed in wild-type cells did not occur in TRPM2KO cells and the induction in wild-type cells is inhibited by chelating Ca^{2+}, suggesting that $[Ca^{2+}]_i$ increases mediated through TRPM2 lead to HO-1 expression. Bacterial killing in phagosomes is also reported to be regulated by TRPM2 activity [84]. TRPM2 deficiency increases the bacterial burden of *Pseudomonas aeruginosa* (PA) and *Staphylococcus aureus* (SA) in BMDM without affecting phagocytosis. TRPM2 functionally expressed in phagosomal membrane promotes acidification of SA-internalized phagosomes that is a hallmark of phagosomal maturation and is regarded to be crucial for degradation of phagocytosed particles and up-regulation of bacterial killing [88].

Contrary to reports showing that TRPM2 up-regulates inflammation/innate immunity, protective anti-inflammatory roles of TRPM2 were also reported in a LPS-induced lung inflammatory model [89]. After intraperitoneal injection with LPS, TRPM2KO mice had higher mortality with pronounced lung edema than did wild-type mice. Histopathology of tissues from TRPM2KO mice showed increased levels of tissue cytokines including CXCL2, TNFα, IL-6 and myeloperoxidase (MPO) activity, suggesting enhanced neutrophil infiltration in mice lacking TRPM2. ROS release and oxidative DNA damage in TRPM2KO cells are significantly larger than those in wild-type cells, and a TRPM2 inhibitor increased ROS release from wild-type cells that was equivalent to that of TRPM2KO, thus indicating the inhibitory effects of TRPM2 activity. As activity of the electrogenic NOX enzyme is known to be voltage-sensitive [90], membrane depolarization through TRPM2 is suggested to negatively regulate NOX activity, and the absence of this regulatory mechanism in TRPM2KO mice could enhance ROS production and aggravate inflammation. Nonetheless, the role of TRPM2 in immunity remains controversial, and its activation could depend on the stimulus type, particularly since immunogens can activate multiple cascades (**Table 1**). In addition, immune reactivity is strongly related to body temperature [83, 91]. Thus, the temperature dependence of TRPM2 must be considered [19]. Outcomes could also be affected depending on the extent of TRPM2 activity, e.g., Ca^{2+} influx through TRPM2 could be beneficial for many Ca^{2+}-dependent events, whereas large Ca^{2+} influx could cause Ca^{2+} overload.

TRPM2 is also known to contribute to the regulation of blood glucose levels (**Figure 4**) likely because of its functional expression in pancreatic β-cells [92], which secrete insulin in response to elevated blood glucose. Although the primary pathway of glucose-stimulated insulin secretion is through ATP-sensitive K^+ (K_{ATP}) channel closure and L-type voltage-gated Ca^{2+} channel activation to increase $[Ca^{2+}]_i$, many other ion channels, including TRPM2, are reported to be involved in $[Ca^{2+}]_i$-increases to evoke insulin secretion [93]. ROS are produced in response to extracellular signals such as insulin, cytokines, hormones and blood glucose elevation in pancreatic β-cells [94, 95]. In addition, expression of the antioxidant enzyme catalase and glutathione reductase in the pancreas is very low [96], indicating that the intracellular redox state of β-cells could be affected at a physiological level by the systemic metabolic state. Intracellular Ca^{2+}-oscillations evoked by high glucose concentrations are attenuated in TRPM2KO pancreatic β-cells [97]. In

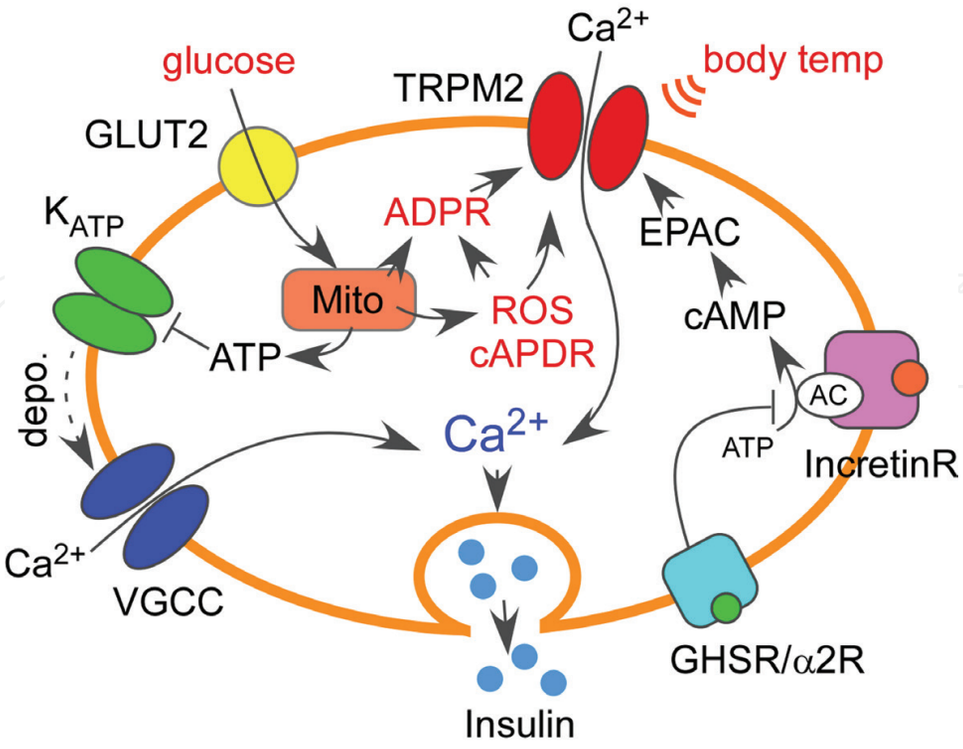


Figure 4. Functional involvement of TRPM2 in regulating insulin secretion from pancreatic β-cells. GLUT2, glucose transporter 2; K_{ATP}, ATP-sensitive K^+ channel; VGCC, voltage-gated Ca^{2+} channel; GHSR, growth hormone secretagogue receptor; α2R, α2 adrenergic receptor; IncretinR, incretin receptor; EPAC, exchange protein directly activated by cAMP; Mito, mitochondria.

addition, heat-evoked responses in Wt b-cells were enhanced by H_2O_2 in a dose-dependent manner, however, TRPM2KO cells completely lacked the response [20]. Glucose-stimulated insulin secretion from pancreatic islets was attenuated by TRPM2 deficiency [97], and the N-acetyl cysteine-sensitive fraction of glucose-stimulated insulin secretion was increased by temperature elevation from 33 °C to 40 °C in wild type, but not TRPM2KO cells, suggesting insulin secretion could be up-regulated by ROS and temperature-dependent TRPM2 activity [20]. TRPM2KO mice show blunted insulin secretion and higher blood glucose levels in oral and intraperitoneal glucose tolerance tests relative to wild-type mice, which highlights TRPM2 function in blood glucose regulation *in vivo* [97].

TRPM2 could also be involved in hormone-regulated insulin secretion. Glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are incretin hormones released from the intestine to enhance glucose-stimulated insulin secretion from pancreatic islets [98]. The up-regulation of insulin release by incretin was shown to be TRPM2-dependent [97, 99]. This increase in insulin secretion is mediated by generation of cAMP and activation of exchange protein directly activated by cAMP (EPAC). By inhibiting the same pathway, insulinostatic effects of ghrelin and adrenaline are reportedly achieved [100, 101]. Although the involvement of ROS-evoked TRPM2 activity in such hormone-regulated insulin secretion has not been defined, TRPM2 participation in glucose metabolism seems likely. In contrast, TRPM2-mediated aggravation of inflammation was reported to cause insulin resistance in peripheral tissues [102]. High-fat diet (HFD)-induced obesity, chronic inflammation and insulin

resistance with elevated plasma and tissue cytokines are also reported to be related [103]. TRPM2KO mice show resistance to HFD-induced obesity, as well as lower cytokine levels and macrophage infiltration in adipose tissue compared with wild-type mice [102]. Energy expenditure and glucose uptake to muscle and heart are higher in TRPM2KO mice than in wild-type animals, and this increase is accompanied by elevated expression levels of metabolic and mitochondrial genes. These data suggest that, in addition to regulating insulin secretion, TRPM2 could control glucose metabolism in glucose-consuming tissues.

6. Conclusions

Several TRP channels, particularly TRPA1 and TRPM2, are redox-sensitive and play important roles in both physiological and pathophysiological phenomena that involve redox signals. Therefore, TRPA1 and TRPM2 would be promising targets to develop medicines to treat redox-related diseases.

Author details

Makiko Kashio[1] and Makoto Tominaga[2]*

*Address all correspondence to: tominaga@nips.ac.jp

1 Department of Physiology, Aichi Medical University, Aichi, Japan

2 Department of Cell Physiology, Okazaki Institute for Integrative Biosciences, Okazaki, Japan

References

[1] Droge W. Free radicals in the physiological control of cell function. Physiological Reviews. 2002;**82**(1):47-95

[2] Rhee SG. Cell signaling. H_2O_2, a necessary evil for cell signaling. Science. 2006;**312**(5782): 1882-1883

[3] Brown DI, Griendling KK. Nox proteins in signal transduction. Free Radical Biology and Medicine. 2009;**47**(9):1239-1253

[4] Roos D, et al. Mutations in the X-linked and autosomal recessive forms of chronic granulomatous disease. Blood. 1996;**87**(5):1663-1681

[5] Ramsey IS, Delling M, Clapham DE. An introduction to TRP channels. Annual Review of Physiology. 2006;**68**:619-647

[6] Gaudet R. TRP channels entering the structural era. The Journal of Physiology. 2008; **586**(15):3565-3575

[7] Constantine M, et al. Heterologously-expressed and liposome-reconstituted human transient receptor potential melastatin 4 channel (TRPM4) is a functional tetramer. Scientific Reports. 2016;**6**:19352

[8] Gaudet R. A primer on ankyrin repeat function in TRP channels and beyond. Molecular BioSystems. 2008;**4**(5):372-379

[9] Stokes A, et al. TRPA1 is a substrate for de-ubiquitination by the tumor suppressor CYLD. Cellular Signalling. 2006;**18**(10):1584-1594

[10] Doerner JF, et al. Transient receptor potential channel A1 is directly gated by calcium ions. The Journal of Biological Chemistry. 2007;**282**(18):13180-13189

[11] Zurborg S, et al. Direct activation of the ion channel TRPA1 by Ca^{2+}. Nature Neuroscience. 2007;**10**(3):277-299

[12] Wang YY, et al. The nociceptor ion channel TRPA1 is potentiated and inactivated by permeating calcium ions. The Journal of Biological Chemistry. 2008;**283**(47):32691-32703

[13] Perraud AL, et al. ADP-ribose gating of the calcium-permeable LTRPC2 channel revealed by Nudix motif homology. Nature. 2001;**411**(6837):595-599

[14] Iordanov I, et al. The proposed channel-enzyme transient receptor potential melastatin 2 does not possess ADP ribose hydrolase activity. eLife. 2016;**5**:e17600

[15] Toth B, Iordanov I, Csanady L. Putative chanzyme activity of TRPM2 cation channel is unrelated to pore gating. Proceedings of the National Academy of Sciences of the United States of America. 2014;**111**(47):16949-16954

[16] Toth B, Iordanov I, Csanady L. Ruling out pyridine dinucleotides as true TRPM2 channel activators reveals novel direct agonist ADP-ribose-2′-phosphate. The Journal of General Physiology. 2015;**145**(5):419-430

[17] Hara Y, et al. LTRPC2 Ca^{2+}-permeable channel activated by changes in redox status confers susceptibility to cell death. Molecular Cell. 2002;**9**(1):163-173

[18] Knowles H, Li Y, Perraud AL. The TRPM2 ion channel, an oxidative stress and metabolic sensor regulating innate immunity and inflammation. Immunologic Research. 2013;**55**(1-3):241-248

[19] Kashio M, et al. Redox signal-mediated sensitization of transient receptor potential melastatin 2 (TRPM2) to temperature affects macrophage functions. Proceedings of the National Academy of Sciences of the United States of America. 2012;**109**(17):6745-6750

[20] Kashio M, Tominaga M. Redox signal-mediated enhancement of the temperature sensitivity of Transient receptor potential melastatin 2 (TRPM2) elevates glucose-induced insulin secretion from pancreatic islets. The Journal of Biological Chemistry. 2015;**290**(19):12435-12442

[21] McHugh D, et al. Critical intracellular Ca^{2+} dependence of transient receptor potential melastatin 2 (TRPM2) cation channel activation. The Journal of Biological Chemistry. 2003;**278**(13):11002-11006

[22] Csanady L, Torocsik B. Four Ca^{2+} ions activate TRPM2 channels by binding in deep crevices near the pore but intracellularly of the gate. The Journal of General Physiology. 2009;**133**(2):189-203

[23] Du J, Xie J, Yue L. Modulation of TRPM2 by acidic pH and the underlying mechanisms for pH sensitivity. The Journal of General Physiology. 2009;**134**(6):471-488

[24] Sumoza-Toledo A, Penner R. TRPM2: A multifunctional ion channel for calcium signalling. The Journal of Physiology. 2011;**589**(Pt 7):1515-1525

[25] Sumoza-Toledo A, et al. Dendritic cell maturation and chemotaxis is regulated by TRPM2-mediated lysosomal Ca^{2+} release. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2011;**25**(10):3529-3542

[26] Manna PT, et al. TRPM2-mediated intracellular Zn^{2+} release triggers pancreatic beta-cell death. The Biochemical Journal. 2015;**466**(3):537-546

[27] Nakamura K. Central circuitries for body temperature regulation and fever. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2011;**301**(5): R1207–R1228

[28] Song K, et al. The TRPM2 channel is a hypothalamic heat sensor that limits fever and can drive hypothermia. Science. 2016;**353**(6306):1393-1398

[29] Tan CH, McNaughton PA. The TRPM2 ion channel is required for sensitivity to warmth. Nature. 2016;**536**(7617):460-463

[30] Bautista DM, et al. TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents. Cell. 2006;**124**(6):1269-1282

[31] Hinman A, et al. TRP channel activation by reversible covalent modification. Proceedings of the National Academy of Sciences of the United States of America. 2006; **103**(51):19564-19568

[32] Andersson DA, et al. Transient receptor potential A1 is a sensory receptor for multiple products of oxidative stress. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2008;**28**(10):2485-2494

[33] Macpherson LJ, et al. Noxious compounds activate TRPA1 ion channels through covalent modification of cysteines. Nature. 2007;**445**(7127):541-545

[34] Bessac BF, et al. TRPA1 is a major oxidant sensor in murine airway sensory neurons. The Journal of Clinical Investigation. 2008;**118**(5):1899-1910

[35] Miyamoto T, et al. TRPV1 and TRPA1 mediate peripheral nitric oxide-induced nociception in mice. PLoS One. 2009;**4**(10):e7596

[36] Takahashi N, et al. Molecular characterization of TRPA1 channel activation by cysteine-reactive inflammatory mediators. Channels. 2008;**2**(4):287-298

[37] Liebler DC. Protein damage by reactive electrophiles: Targets and consequences. Chemical Research in Toxicology. 2008;**21**(1):117-128

[38] Shimizu S, et al. Sensitization of H_2O_2-induced TRPM2 activation and subsequent interleukin-8 (CXCL8) production by intracellular Fe(2+) in human monocytic U937 cells. The International Journal of Biochemistry and Cell Biology. 2015;**68**:119-127

[39] Schreiber V, et al. Poly(ADP-ribose): Novel functions for an old molecule. Nature Reviews Molecular Cell Biology. 2006;**7**(7):517-528

[40] Fonfria E, et al. TRPM2 channel opening in response to oxidative stress is dependent on activation of poly(ADP-ribose) polymerase. British Journal of Pharmacology. 2004; **143**(1):186-192

[41] Ayub K, Hallett MB. The mitochondrial ADPR link between Ca^{2+} store release and Ca^{2+} influx channel opening in immune cells. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2004;**18**(12):1335-1338

[42] Perraud AL, et al. Accumulation of free ADP-ribose from mitochondria mediates oxidative stress-induced gating of TRPM2 cation channels. The Journal of Biological Chemistry. 2005;**280**(7):6138-6148

[43] Partida-Sanchez S, et al. Chemotaxis of mouse bone marrow neutrophils and dendritic cells is controlled by ADP-ribose, the major product generated by the CD38 enzyme reaction. Journal of Immunology. 2007;**179**(11):7827-7839

[44] Rah SY, et al. ADP-ribose/TRPM2-mediated Ca^{2+} signaling is essential for cytolytic degranulation and antitumor activity of natural killer cells. Scientific Reports. 2015;**5**:9482

[45] Howard M, et al. Formation and hydrolysis of cyclic ADP-ribose catalyzed by lymphocyte antigen CD38. Science. 1993;**262**(5136):1056-1059

[46] Wehage E, et al. Activation of the cation channel long transient receptor potential channel 2 (LTRPC2) by hydrogen peroxide. A splice variant reveals a mode of activation independent of ADP-ribose. The Journal of Biological Chemistry. 2002;**277**(26):23150-23156

[47] Trevisani M, et al. 4-hydroxynonenal, an endogenous aldehyde, causes pain and neurogenic inflammation through activation of the irritant receptor TRPA1. Proceedings of the National Academy of Sciences of the United States of America. 2007;**104**(33):13519-13524

[48] Takahashi N, et al. TRPA1 underlies a sensing mechanism for O_2. Nature Chemical Biology. 2011;**7**(10):701-711

[49] Chen J, et al. Species differences and molecular determinant of TRPA1 cold sensitivity. Nature Communications. 2013;**4**:2501

[50] Miyake T, et al. Cold sensitivity of TRPA1 is unveiled by the prolyl hydroxylation blockade-induced sensitization to ROS. Nature Communications. 2016;**7**:12840

[51] Zhao M, et al. Acute cold hypersensitivity characteristically induced by oxaliplatin is caused by the enhanced responsiveness of TRPA1 in mice. Molecular Pain. 2012;**8**:55

[52] Nassini R, et al. Oxaliplatin elicits mechanical and cold allodynia in rodents via TRPA1 receptor stimulation. Pain. 2011;**152**(7):1621-1631

[53] Barriere DA, et al. Paclitaxel therapy potentiates cold hyperalgesia in streptozotocin-induced diabetic rats through enhanced mitochondrial reactive oxygen species production and TRPA1 sensitization. Pain. 2012;**153**(3):553-561

[54] Paravicini TM, Sobey CG. Cerebral vascular effects of reactive oxygen species: Recent evidence for a role of NADPH-oxidase. Clinical and Experimental Pharmacology and Physiology. 2003;**30**(11):855-859

[55] Sullivan MN, et al. Localized TRPA1 channel Ca^{2+} signals stimulated by reactive oxygen species promote cerebral artery dilation. Science Signaling. 2015;**8**(358):ra2

[56] Aubdool AA, et al. TRPA1 activation leads to neurogenic vasodilatation: Involvement of reactive oxygen nitrogen species in addition to CGRP and NO. British Journal of Pharmacology. 2016;**173**(15):2419-2433

[57] McNulty S, Fonfria E. The role of TRPM channels in cell death. Pflugers Archiv: European Journal of Physiology. 2005;**451**(1):235-242

[58] Sun Y, et al. TRPM2 promotes neurotoxin MPP+/MPTP-induced cell death. Molecular Neurobiology. 2016. Epub ahead of print

[59] Ostapchenko VG, et al. The transient receptor potential melastatin 2 (TRPM2) channel contributes to beta-amyloid oligomer-related neurotoxicity and memory impairment. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2015;**35**(45):5157-5169

[60] Fonfria E, et al. Amyloid beta-peptide(1-42) and hydrogen peroxide-induced toxicity are mediated by TRPM2 in rat primary striatal cultures. Journal of Neurochemistry. 2005;**95**(3):715-723

[61] Roberge S, et al. TNF-alpha-mediated caspase-8 activation induces ROS production and TRPM2 activation in adult ventricular myocytes. Cardiovascular Research. 2014;**103**(1):90-99

[62] Ye M, et al. TRPM2 channel deficiency prevents delayed cytosolic Zn^{2+} accumulation and CA1 pyramidal neuronal death after transient global ischemia. Cell Death and Disease. 2014;**5**:e1541

[63] Hiroi T, et al. Neutrophil TRPM2 channels are implicated in the exacerbation of myocardial ischaemia/reperfusion injury. Cardiovascular Research. 2013;**97**(2):271-281

[64] Gao G, et al. TRPM2 mediates ischemic kidney injury and oxidant stress through RAC1. The Journal of Clinical Investigation. 2014;**124**(11):4989-5001

[65] Gelderblom M, et al. Transient receptor potential melastatin subfamily member 2 cation channel regulates detrimental immune cell invasion in ischemic stroke. Stroke. 2014;**45**(11):3395-3402

[66] Hoffman NE, et al. Ca(2)(+) entry via TRPM2 is essential for cardiac myocyte bioenergetics maintenance. American Journal of Physiology: Heart and Circulatory Physiology. 2015;**308**(6):H637–H650

[67] Miller BA, et al. The second member of transient receptor potential-melastatin channel family protects hearts from ischemia-reperfusion injury. The American Journal of Physiology: Heart and Circulatory Physiology. 2013;**304**(7):H1010–H1022

[68] Miller BA, et al. TRPM2 channels protect against cardiac ischemia-reperfusion injury: Role of mitochondria. The Journal of Biological Chemistry. 2014;**289**(11):7615-7629

[69] Bao L, et al. Depletion of the human ion channel TRPM2 in neuroblastoma demonstrates its key role in cell survival through modulation of mitochondrial reactive oxygen species and bioenergetics. The Journal of Biological Chemistry. 2016;**291**(47):24449-24464

[70] Llorente-Folch I, et al. The regulation of neuronal mitochondrial metabolism by calcium. The Journal of Physiology. 2015;**593**(16):3447*3462

[71] Inada H, Iida T, Tominaga M. Different expression patterns of TRP genes in murine B and T lymphocytes. Biochemical and Biophysical Research Communications. 2006; **350**(3):762-767

[72] Lange I, et al. Synergistic regulation of endogenous TRPM2 channels by adenine dinucleotides in primary human neutrophils. Cell Calcium. 2008;**44**(6):604-615

[73] Yamamoto S, et al. TRPM2-mediated Ca^{2+} influx induces chemokine production in monocytes that aggravates inflammatory neutrophil infiltration. Nature Medicine. 2008;**14**(7): 738-747

[74] Kraft R, et al. Hydrogen peroxide and ADP-ribose induce TRPM2-mediated calcium influx and cation currents in microglia. American Journal of Physiology: Cell Physiology. 2004;**286**(1):C129–C137

[75] Oda S, et al. TRPM2 contributes to antigen-stimulated Ca(2)(+) influx in mucosal mast cells. Pflugers Archiv: European Journal of Physiology. 2013;**465**(7):1023-1030

[76] Haraguchi K, et al. TRPM2 contributes to inflammatory and neuropathic pain through the aggravation of pronociceptive inflammatory responses in mice. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2012;**32**(11):3931-3941

[77] Murakami T, et al. Critical role for calcium mobilization in activation of the NLRP3 inflammasome. Proceedings of the National Academy of Sciences of the United States of America. 2012;**109**(28):11282-11287

[78] Jin C, Flavell RA. Molecular mechanism of NLRP3 inflammasome activation. Journal of Clinical Immunology. 2010;**30**(5):628-631

[79] Zhong Z, et al. TRPM2 links oxidative stress to NLRP3 inflammasome activation. Nature Communications. 2013;**4**:1611

[80] Zhou R, et al. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nature Immunology. 2010;**11**(2):136-140

[81] Shah A, et al. Thioredoxin-interacting protein mediates high glucose-induced reactive oxygen species generation by mitochondria and the NADPH oxidase, Nox4, in mesangial cells. The Journal of Biological Chemistry. 2013;**288**(10):6835-6848

[82] Tseng HH, et al. TRPM2 regulates TXNIP-mediated NLRP3 inflammasome activation via interaction with p47 phox under high glucose in human monocytic cells. Scientific Reports. 2016;**6**:35016

[83] Hasday JD, Fairchild KD, Shanholtz C. The role of fever in the infected host. Microbes and Infection. 2000;**2**(15):1891-1904

[84] Di A, et al. Role of phagosomal redox-sensitive TRP channel TRPM2 in regulating bactericidal activity of macrophages. Journal of Cell Science. 2017;**130**(4):735-744

[85] Knowles H, et al. Transient receptor potential melastatin 2 (TRPM2) ion channel is required for innate immunity against Listeria monocytogenes. Proceedings of the National Academy of Sciences of the United States of America. 2011;**108**(28):11578-11583

[86] Suzue K, et al. In vivo role of IFN-gamma produced by antigen-presenting cells in early host defense against intracellular pathogens. European Journal of Immunology. 2003;**33**(10):2666-2675

[87] Qian X, et al. Transient receptor potential melastatin 2 protects mice against polymicrobial sepsis by enhancing bacterial clearance. Anesthesiology. 2014;**121**(2):336-351

[88] Tjelle TE, Lovdal T, Berg T. Phagosome dynamics and function. BioEssays: News and Reviews in Molecular, Cellular and Developmental Biology. 2000;**22**(3):255-263

[89] Di A, et al. The redox-sensitive cation channel TRPM2 modulates phagocyte ROS production and inflammation. Nature Immunology. 2011;**13**(1):29-34

[90] DeCoursey TE, Morgan D, Cherny VV. The voltage dependence of NADPH oxidase reveals why phagocytes need proton channels. Nature. 2003;**422**(6931):531-534

[91] Blatteis CM. Fever: Is it beneficial? The Yale Journal of Biology and Medicine. 1986; **59**(2):107-116

[92] Togashi K, et al. TRPM2 activation by cyclic ADP-ribose at body temperature is involved in insulin secretion. The EMBO Journal. 2006;**25**(9):1804-1815

[93] Islam MS. Calcium signaling in the islets. Advances in Experimental Medicine and Biology. 2010;**654**:235-259

[94] Paulsen CE, Carroll KS. Orchestrating redox signaling networks through regulatory cysteine switches. ACS Chemical Biology. 2010;**5**(1):47-62

[95] Pi J, et al. Reactive oxygen species as a signal in glucose-stimulated insulin secretion. Diabetes. 2007;**56**(7):1783-1791

[96] Lenzen S, Drinkgern J, Tiedge M. Low antioxidant enzyme gene expression in pancreatic islets compared with various other mouse tissues. Free Radical Biology and Medicine. 1996;**20**(3):463-466

[97] Uchida K, et al. Lack of TRPM2 impaired insulin secretion and glucose metabolisms in mice. Diabetes. 2011;**60**(1):119-126

[98] Leech CA, et al. Molecular physiology of glucagon-like peptide-1 insulin secretagogue action in pancreatic beta cells. Progress in Biophysics and Molecular Biology. 2011;**107**(2):236-247

[99] Yoshida M, et al. Involvement of cAMP-EPAC-TRPM2 activation in glucose- and incretin-induced insulin secretion. Diabetes. 2014 ;**63**(10):3394-3403

[100] Kurashina T, et al. The beta-cell GHSR and downstream cAMP/TRPM2 signaling account for insulinostatic and glycemic effects of ghrelin. Scientific Reports. 2015;**5**:14041

[101] Ito K, et al. Endogenous alpha2A-adrenoceptor-operated sympathoadrenergic tones attenuate insulin secretion via cAMP/TRPM2 signaling. Diabetes. 2016;**66**(3):699-709

[102] Zhang Z, et al. TRPM2 Ca^{2+} channel regulates energy balance and glucose metabolism. American Journal of Physiology. Endocrinology and Metabolism. 2012;**302**(7):E807–E816

[103] Xu H, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. The Journal of Clinical Investigation. 2003;**112**(12): 1821-1830

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