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Review

Sensing of redox status by TRP channels

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ABSTRACT

Cellular redox status is maintained by the balance between series of antioxidant systems and production of reactive oxygen/nitrogenous species. Cells utilize this redox balance to mediate diverse physiological functions. Transient receptor potential (TRP) channels are non-selective cation channels that act as biosensors for environmental and noxious stimuli, such as capsaicin and allicin, as well as changes in temperature and conditions inside the cell. TRP channels also have an emerging role as essential players in detecting cellular redox status to regulate cellular signals mediating physiological phenomena. Reactive species activate TRP channels either directly through oxidative amino acid modifications or indirectly through second messengers. For instance, TRPA1, TRPV1 and TRPC5 channels are directly activated by oxidizing agents through cysteine modification; whereas, TRPM2 channel is indirectly activated by production of ADP-ribose. One intriguing property of several TRP channels is susceptibility to both oxidizing and reducing stimuli, suggesting TRP channels could potentially act as a bidirectional sensor for detecting deviations in redox status. In this review, we discuss the unique chemical physiologies of redox sensitive TRP channels and their physiological significance in Ca^{2+} signaling.

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Contents

1. TRP channels as sensors of cellular redox status

The evolution of organism to utilize molecular O_2 in the atmosphere inevitably led to constant production of reactive oxygen species (ROS) by cells as a byproduct of oxidative respiration. Cellular redox status is maintained by the balance between a series of antioxidant systems and production of ROS and reactive nitrogenous species (RNS). It is believed that cellular antioxidants evolved in order to protect cells from oxidative damage mediated by ROS. There are two main axes of cellular reductants: the glutathione axis,

Abbreviations: ADPR, ADP-ribose; AITC, allyl isothiocyanate; ARD, ankyrin repeat domain; CXCL2, chemokine (C-X-C motif) ligand 2; CXCL8, interleukin-8; Cys, Cysteine; DSS, dextran sulfate sodium; NAD^+, nicotinamide adenine dinucleotide; PLC, phospholipase C; RNS, reactive nitrogenous species; ROS, reactive oxygen species; SNAP, *S*-nitroso-*N*-acetylpenicillamine; TRP, transient receptor potential.

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consisting of glutathione, glutaredoxin and glutathione peroxidase; the peroxiredoxin axis consisting of peroxiredoxin, thioredoxin and thioredoxin reductase [1]. Sulfhydryl (SH) groups on cysteine (Cys) residues allow these proteins to reduce oxidized proteins, which are sequentially oxidized down the axes until final reduction by NADPH. ROS are the reactive derivatives of O_2, including hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$) and superoxide ($O^{\bullet -}$) and are produced by the mitochondrial electron transport chain and NADPH oxidase [2,3]. RNS includes nitric oxide (NO) and the more reactive peroxynitrite ($ONOO^-$), which are generated as a result of enzymatic NO synthase activity [4,5].

The initial conception of ROS as damaging and harmful molecules has led to most of the subsequent studies in the field of redox biology placing emphasis on reactive species as a manifestation of pathology and/or target of pharmacological intervention. When production of ROS exceeds the reductive capacity of antioxidants available within cells, ROS non-specifically react with proteins, lipids and nucleic acids. Indeed, excessive ROS production and consequent oxidative damages are implicated in various diseases such as atherosclerosis, cancer, neurodegenerative diseases, rheumatoid arthritis and hypertension [6–8]. However, whether ROS are involved in the etiology of these diseases remains controversial primarily due to inconsistent outcome of antioxidants therapy to ameliorate symptoms of these diseases [9–12]. Deviating from the idea of ROS as toxic byproducts, recent research has revealed that ROS also act as signaling molecules, essential to mediating physiological phenomena including immune responses, signal transduction, cell proliferation and regulation of vascular tone [3,6,8]. Therefore, in order to obtain more holistic and complete understanding of redox biology, it is crucial to characterize both physiological and pathological implications of redox status alterations.

Various proteins, including ion channels, kinases and transcription factors, detect alterations in cellular redox status [13–16]. Redox-sensitive ion channels play a particularly vital role in sensing acute changes in the redox status by exploiting rapid activation kinetics to change membrane potential and intracellular ionic content. Amongst these channels, transient receptor potential (TRP) channels have emerged as acute sensors of redox status, playing an essential role in signal transduction by rapidly converting changes in redox status to Na^+ influx for membrane depolarization and Ca^{2+} influx to deliver a potent intracellular second messenger Ca^{2+} in the cytoplasm [8].

TRP channels are non-selective cation channels first cloned from *Drosophilia melanogaster* [17]. Categorized by degree of amino acid sequence homology, mammalian TRP channels are divided into six subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPA (ankyrin), TRPP (polycystic kidney disease) and TRPML (mucolipin) [18,19]. In general, TRP channels have a tetrameric structure in which four protein subunits assemble to form a complex with fourfold symmetry [20]. Tetramers may be comprised of combination of identical or different TRP proteins depending on the channel [21–23]. Each TRP protein subunit consists of six transmembrane regions and a pore-forming region between the fifth and sixth transmembrane region, C- and N-terminals facing the cytoplasm. Most TRP channels are activated by multiple stimuli, thus functioning as polymodal sensors. TRPC channels are receptor-activated Ca^{2+}-permeable cation channels regulated by diacylglycerol and phosphatidylinositol-4,5-bisphophate (PIP_2) which are the downstream product and the upstream substrate of phospholipase C (PLC) activation, respectively [24,25]. TRPV channels are characterized by robust sensitivity to heat [26]. The founding member of mammalian TRPV channels, TRPV1 is the receptor for capsaicin and is activated by temperatures above >43 °C and acidic pH (pH < 6.5), and regulated by PIP_2 [27–29]. TRPM channels are characterized by the presence of a functional protein domain in their C-termini. For instance, TRPM6 and TRPM7 carry serine/thereonine-protein kinases, while TRPM2 possesses a nudix-type motif 9-homology (NUDT9-H) domain in its C-terminus [30]. TRPM8 is responsive to cold and menthol [31,32]. TRPA1, the only member of the mammalian TRPA subfamily, is another cold sensor, which is activated by electrophiles following covalent modification of Cys residues localized within the ankyrin repeat domain (ARD) [33,34]. In addition to their respective activating stimuli, many of these TRP channels are also activated by alternations in redox environment. Indeed, TRPM2, TRPM7, TRPV1, TRPC5 and TRPA1 are sensitive to various redox-regulating compounds.

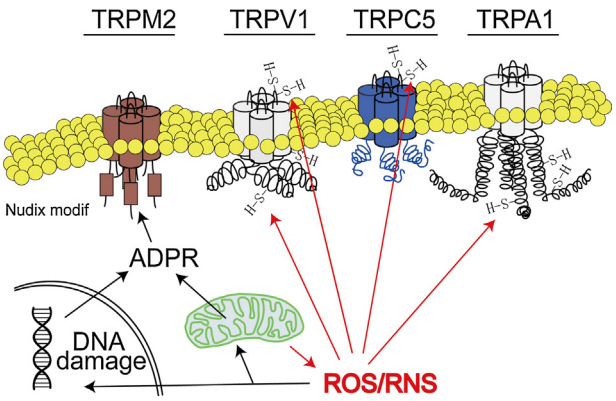

Fig. 1. TRP channels are activated directly or indirectly *via* reactive species.

2. Activation mechanism of redox sensitive TRP channels

2.1. Hydrogen peroxide activates TRPM2 indirectly through stimulation of ADPR production

TRPM2 channels are activated by binding of intracellular ADP-ribose (ADPR) to the C-terminal NUDT9-H motif [35,36]. Although the NUDT9 protein is an ADPR pyrophosphatase that catalyzes conversion of ADPR into AMP and ribose-5-phosphate, the NUDT9-H motif of TRPM2 shows substantially lower enzymatic activity. This suggests binding, rather than enzymatic activity, is important for activation of TRPM2 by ADPR [37–40]. We reported that H_2O_2, ubiquitous and membrane-diffusible ROS, evoked a robust Ca^{2+} influx in both TRPM2-expressing human embryonic kidney (HEK293) cells and insulin-secreting pancreatic/islet tumor cells (RIN-5F) natively expressing TRPM2 [41]. Activation of TRPM2 by H_2O_2 has subsequently been observed in pancreatic β-cells [42,43], hippocampal neurons [44,45], endothelial cells [46], microglia [47], U937 human monocytes [48,49], hepatocytes [50], cardiomyocytes [51,52] and neutrophils [53].

Activation of TRPM2 by H_2O_2 is thought to occur indirectly through production of ADPR and consequent stimulation of the C-termini NUDT9-H motif [39] based on several observations (Fig. 1). First, application of H_2O_2 leads to rapid production of nicotinamide adenine dinucleotide (NAD^+), which is enzymatically converted within mitochondria and nuclei to poly(ADPR) and then ADPR [54,55]. Second, displacement of cytoplasmic content with a pipette or extracellular solution using patch clamp prevented H_2O_2 from inducing TRPM2 activation [41,56]. Third, pharmacological inhibition of NAD^+ or ADPR synthesis, and overexpression of cytoplasmic or mitochondrial ADPR pyrophosphatase suppressed the H_2O_2-evoked Ca^{2+} influx mediated by TRPM2 [39,57]. Finally, TRPM2-expressing DT40 lymphocytes deficient in poly(ADPR) polymerase, an enzyme mediating conversion of NAD^+ to poly(ADPR), showed a lack of Ca^{2+} influx following H_2O_2 application [58]. Collectively, these lines of evidence convincingly suggest

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