Chapter 29
TRP Channels as Mediators of Oxidative Stress

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Abstract The transient receptor potential (TRP) protein superfamily is a diverse group of cation-permeable channels expressed in mammalian cells, which is divided into six subfamilies based on sequence identity. Three subfamilies have members with roles in oxidative stress: the TRPC subfamily characterized by receptor operated calcium entry channels; the TRPM subfamily with a number of members involved in cell proliferation and death; and the TRPV subfamily which is activated by chemical, mechanical, and physical stimuli. The TRPC members TRPC3 and TRPC4 can serve as subunits of a redox-sensitive ion channel in native aortic endothelial cells. The TRPM family member TRPM2 has a number of physiologic isoforms expressed in many cell types and responds to stimuli including oxidative stress, TNFα, and β-amyloid peptide. The important role of TRPM2 isoforms in cell proliferation and oxidant-induced cell death has been well established using divergent cell systems and techniques including overexpression, channel depletion or inhibition, and calcium chelation. TRPM7 has been shown to be involved in Ca^{2+} influx and anoxic cell death in cortical neurons. In these cells and in B cells, precise expression of TRPM7 is necessary for cell survival. TRPV1 is involved in oxidant stress-induced pain and in neuronal injury, contributing to diabetic sensory neuropathy. Future studies will likely identify additional channels involved in oxidant injury, as well as better define mechanisms through which these channels are regulated and mediate their effects. Therapeutic approaches to modulate activation of specific TRP channels are likely to have an important impact in reducing tissue damage in a number of diseases resulting from oxidant stress including ischemia/reperfusion injury and diabetes.

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29.1 Introduction

The transient receptor potential (TRP) protein superfamily is a diverse group of calcium-permeable cation channels expressed in mammalian cells [1–5]. Mammalian TRP channels have been organized into six protein subfamilies designated C (canonical), V (vanilloid receptor), M (melastatin), A (ANKTM), P (polycystin), and ML (mucolipin). Mammalian isoforms have six putative transmembrane domains similar to the structure of many pore-forming subunits of voltage-gated channels. While many of them lack positively charged residues necessary for the voltage sensor and are voltage independent, some TRP channels, particularly those which are temperature sensitive, are voltage gated [6, 7]. TRP channels function as homotetramers or heterotetramers, with the pore formed by loops between the fifth and six transmembrane domains. Regulation of TRP channels includes roles for (1) extracellular signals, (2) second messengers, (3) channel subunit assembly, and (4) macromolecular complex formation. All TRP channels have multiple protein interaction motifs and regulatory domains including protein kinase A, C, and tyrosine phosphorylation sites. These channels function in many physiological processes and have roles in a number of diseases involving the cardiovascular, endocrine, neurologic, immune, respiratory, gastrointestinal, and reproductive systems as well as kidney, skeletal muscle, and bone [5, 8].

Tissue damage resulting from oxidative stress plays an important role in a number of physiological processes including aging, cancer, neurodegenerative disorders, diabetes mellitus, atherosclerosis, ischemia/reperfusion injury, and autoimmune disease [9, 10]. Oxidative stress results from a disturbance in the balance between oxidants and anti-oxidants, which may lead to tissue injury depending on severity and duration [9, 11]. Reactive oxygen species (ROS) are produced naturally during respiration by the mitochondrial electron transport chain, following activation of the arachidonic acid cascade in the cytosol, and after exposure to ionizing radiation, cytotoxic drugs, or infections which activate neutrophils or phagocytes. Free radical intermediates which are produced include ROS (superoxide anion, hydrogen peroxide, hydroxyl radical) and reactive nitrogen species (RNS; nitric oxide and its derivatives). These radicals damage cells through DNA and protein oxidation and lipid peroxidation. ROS are reduced naturally by antioxidant enzymes including catalase, superoxide dismutases, and glutathione peroxidase, and biological antioxidants include α-tocopherol and absorbic acid. A number of complex signaling events are activated in oxidative stress including enzymes such as phospholipases and protein kinases [12, 13]. Hydrogen peroxide (H_2O_2) induces apoptosis through multiple mechanisms including upregulation of Fas/Fas ligand, which activates the extrinsic cell death pathway, and activation of mitochondrial cell death pathways through modulation of the mitochondrial permeability transition pore (PT) [13–15]. H_2O_2 stimulates an increase in intracellular free calcium ($[Ca^{2+}]_i$), resulting in elevated mitochondrial matrix Ca^{2+}, which together with arachidonic acid, produced by activation of phospholipase A2, opens the mitochondrial PT pore [14, 16]. Activation of the PT pore uncouples oxidative phosphorylation, prevents ATP production, and enhances cytochrome c release into the cytosol. Cytochrome c binds to Apaf-1

(apoptotic protease activating factor 1), forming the apoptosome, activating caspase 9, followed by 3 and 7, and inactivating PARP, contributing to cell death. The rise in $[Ca^{2+}]_i$ may contribute to cell death through a number of pathways in addition to caspase cleavage, PARP inactivation and release of cytochrome c, including activation of tyrosine kinases and phosphatases, and binding of transcription factors to target genes. H_2O_2 has been proposed to mediate an increase in $[Ca^{2+}]_i$ through a number of different mechanisms including voltage-dependent calcium channels and Na^+–Ca^{2+} exchange. The role of TRP channel activation in oxidative stress will be reviewed here.

29.2 TRPC in Oxidative Stress

TRP channels were first shown to have a role in anoxic cell death in *Drosophila.* Whereas anoxia, treatment with mitochondrial uncouplers, or ATP depletion rapidly activated the *Drosophila* channels TRP and TRPL in the dark, mutation of both TRP and TRPL eliminated Ca^{2+} influx in photoreceptor cells in response to anoxia, demonstrating the role of these channels as targets of oxidative stress [17]. Furthermore, constitutive activation of these channels resulted in massive photoreceptor cell death in vivo [18].

The most closely related TRP subfamily to *Drosophila* is that of TRPC. Members are activated by stimulation of G-protein-coupled receptors and receptor tyrosine kinases with ligand, which activates phospholipase C and results in production of inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). A number of models of TRPC activation through PLC-mediated pathways have been proposed [1–3, 13, 19]. Regulation of TRPC cell surface expression is one critical component of channel activation [20, 21]. TRPC channels assemble based on structural similarities reflected in phylogenetic relationships, but specific molecular determinants for subunit assembly have not been identified [3]. While heteromeric channel formation is well established for TRPC 1/4/5 and TRPC 3/6/7 [22–24], multimerization of TRPC is complex and controversial. Different homo- and heteromeric assemblies are possible, and up to three isoforms may contribute to native pore complex formation [4, 25, 26].

Two TRPC channels, TRPC3 and TRPC4, have been shown to be important in oxidant activation of cation current in porcine endothelial cells [27, 28]. ROS cause a sustained increase in $[Ca^{2+}]_i$, resulting in protease activation, changes in the cytoskeleton, and endothelial cell dysfunction [8, 29]. TRPC3 and TRPC4 are expressed and reported to associate endogenously to form a cation-conducting pore complex in these cells. This finding was supported by several approaches including coimmunoprecipitation, FRET, and the observation that endogenous oxidant stress-mediated calcium conductance is suppressed in these cells by dominant negative TRPC3 and TRPC4 mutants [28]. Oxidant stress may also modulate TRPC function though disruption of caveolin 1-rich lipid rafts [30]. In addition, TRP channels can act as NO sensors in endothelial cells [31]. NO can activate TRPC1, TRPC4,

TRPC5, TRPV1, TRPV3, and TRPV4, inducing calcium entry into cells. The physiological significance of ROS and RNS activation of TRPC3/4 in endothelial cells is under investigation. However, because TRP channels may play an important role in oxidant-induced endothelial injury, they should be considered as potential targets to prevent oxidant stress-induced vascular damage.

29.3 TRPM in Oxidative Stress

The TRP channel TRPM subfamily is named after the first described member, TRPM1 (melastatin), a putative tumor suppressor protein [32]. TRPM1 is expressed on melanocytes, and its expression level correlates inversely with melanoma aggressiveness and the potential for metastasis, suggesting a role for this channel in cell proliferation or migration. Other members of the TRPM subfamily also have important roles in cell proliferation and survival including TRPM2 [33, 34], TRPM5 [35], TRPM7 [36], and TRPM8 [37]. Members of the TRPM subfamily share a region of high coiled coil character (CCR) in the C-terminus, which may play a role in ion channel multimerization or in recruitment of regulatory proteins [38]. The C-terminus of these channels displays considerable variability and three of these channels have unique C-terminal enzymatic domains, TRPM2, TRPM6, and TRPM7. These channels function primarily as homotetramers. However, for several TRPM channels, splice variants have been described which inhibit full-length channel function and consist only of N-terminal (TRPM1), C-terminal (TRPM2-TE), or N-terminal and truncated transmembrane domains (TRPM2-S) [34, 39–41]. A role for two of these channels, TRPM2 and TRPM7, in oxidative stress-induced cell death has been extensively studied and will be reviewed here.

29.3.1 TRPM2

TRPM2 is the second member of the TRPM subfamily to be cloned. It is expressed in many cell types including brain, hematopoietic cells, heart, vascular smooth muscle, endothelial cells, lung, endocrine system, and the gastrointestinal tract [29, 34, 42–45]. TRPM2 channels are permeable to sodium, potassium, and calcium. Extracellular signals known to activate TRPM2 include oxidative stress, TNFα, amyloid β-peptide, and concavalin A [33, 46–50]. Stimulation with these extracellular signals results in sufficient production of ADP-ribose (ADPR) to activate TRPM2 by binding to the TRPM2 COOH-terminal NUDT9-H domain, a mitochondrial ADPR hydrolase (Fig. 29.1; modified from Miller) [13, 48, 51, 52]. Cyclic adenosine diphosphoribose (cADPR) can also gate TRPM2 by itself at high concentrations and potentiates the effects of ADPR at lower concentrations [51]. ADPR may arise from a mitochondrial source [52] or via activation of poly (ADPR) polymerase (PARP) [53, 54]. PARP-1 covalently attaches ADPR polymers to proteins, which are then hydrolyzed into free ADPR by PARG [55]. Most evidence supports

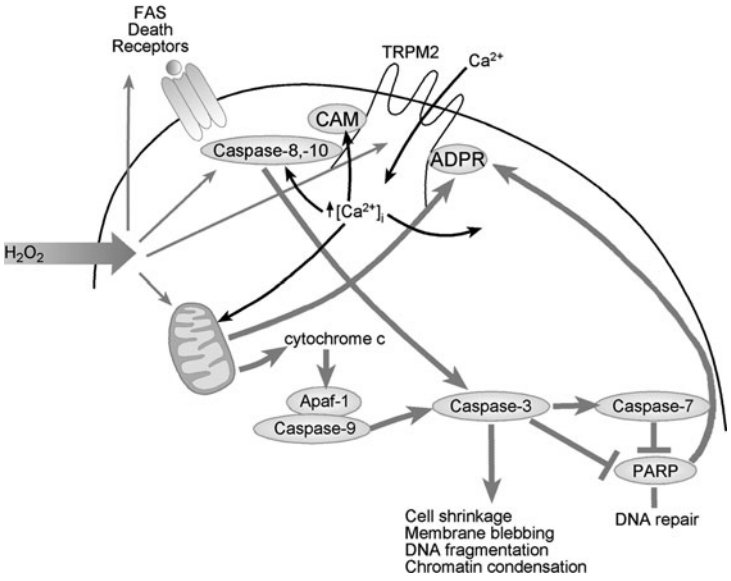

Fig. 29.1 Proposed signaling mechanisms of TRPM2 activation and induction of cell death by H_2O_2. H_2O_2 activates production of ADP-ribose (ADPR) in the mitochondria, which is released into the cytosol, and through activation of PARP/PARG. The increase in ADPR activates TRPM2 by binding to the C-terminal NUDT9-H domain. Ca^{2+} influx ensues, which enhances calmodulin (CAM) binding to TRPM2 and further channel opening. $[Ca^{2+}]_i$ rises, and in association with other oxidative stress-induced signals results in activation of extrinsic and intrinsic cell death pathways, leading to caspase-3 activation and PARP cleavage and inactivation

the conclusion that it is the binding of ADPR to the NUDT9-H domain that is critical for ADPR activation of TRPM2 rather than enzymatic activity of NUDT9-H, because ADPRase activity is low [52, 56]. While nicotinamide adenine dinucleotide (NAD) has been reported to directly induce opening of TRPM2, much evidence suggests this is secondary to conversion to or contamination by ADPR. TRPM2 currents are dependent on and positively regulated by Ca^{2+}, and have a strong requirement for Ca^{2+} at the intracellular surface of the plasma membrane [57, 58]. Low-level activation is seen at 100 nm $[Ca^{2+}]_i$ and maximal activation at 600 nm [57]. Interaction of ADPR with TRPM2 supports limited calcium entry through TRPM2, and Ca^{2+}-bound calmodulin increases. Interaction between calmodulin and an IQ-like motive in the N-terminus of TRPM2 is strengthened, providing positive feedback for TRPM2 activation leading to increased Ca^{2+} influx and enhanced $[Ca^{2+}]_i$ [59]. Recent evidence suggests that TRPM2 with mutant ADPR binding sites can still be activated by $[Ca^{2+}]_i$, and that TRPM2 may be activated under a wide range of physiological conditions through this mechanism [58].

Experimental data from a number of groups concur that oxidative stress results in Ca^{2+} influx through TRPM2 opening, and increased susceptibility to cell death [33, 34, 55, 60, 61]. The mechanisms through which the increase in $[Ca^{2+}]_i$ results in

enhanced cell death were explored in the human monocytic cell line U937, in which TRPM2 isoform expression was modulated with retroviral infection (Fig. 29.1) [62]. Full length TRPM2 (TRPM2-L) activation by oxidative stress results in a significant increase in $[Ca^{2+}]_i$, and decreased cell viability. Procaspases-8, -9, -3, and -7 and PARP were cleaved, demonstrating a signaling cascade involving intrinsic (caspase-9) and extrinsic (caspase-8) cell death pathways. PARP, an important protective mechanism involved in DNA repair, was inactivated [53, 54]. These pathways have previously been linked to H_2O_2-induced apoptosis [63, 64]. This data suggests a feedback loop in which TRPM2 is activated by PARP, but TRPM2 activation in turn results in PARP cleavage and inactivation. Inhibition of the rise in $[Ca^{2+}]_i$ with the intracellular Ca^{2+} chelator BAPTA blocked caspase and PARP cleavage in TRPM-2 expressing cells, demonstrating the importance of the rise in $[Ca^{2+}]_i$ in activation of the cell death cascade.

TRPM channels function as tetramers, and subunit composition is an important factor in regulation of TRPM channel opening. Five physiological splice variants of TRPM2 have been identified: TRPM2-L (full-length or wild type), TRPM2-S (short) [34], TRPM2-ΔN [47], TRPM2-ΔC [47], and TRPM2-TE (tumor-enriched) [41] (Fig. 29.2; modified from Miller, 2006) [13]. TRPM2-S has a deletion of the entire C-terminus including four of six C-terminal transmembrane domains and the putative calcium pore [34]. TRPM2-S suppresses Ca^{2+} influx through TRPM2-L and inhibits cell death induced by oxidative stress [34, 62]. The mechanisms through which TRPM2-S inhibits TRPM2-L function are not known. However, because TRPM2-S co-associates with TRPM2-L, one hypothesis is that TRPM2-S participates in heterodimer formation, altering the tertiary structure of the TRPM2 tetramer required for ion permeability. TRPM2-ΔN has a deletion of amino acids 538-557 in the N-terminus and fails to respond to hydrogen peroxide (H_2O_2) or ADPR, suggesting that TRPM2-ΔN dominantly disrupts channel gating or assembly. TRPM2-ΔC has a deletion of amino acids 1292-1325 in the C-terminus, decreasing affinity for ADPR [47]. Cells expressing TRPM2-ΔC do not respond to ADPR but do response to H_2O_2, suggesting that oxidative stress can activate TRPM2 through mechanisms independently of ADPR [47, 51, 58]. TRPM2-TE was identified by investigators utilizing antisense technology to identify tumor suppressor genes [41]. Two TRPM2-TE transcripts were found which encode either a 218 amino acid, 25 kDa protein or a 184 amino acid, 21 kDa protein (TRPM2-TE-ΔC). These proteins are highly expressed in tumor cells including melanoma and lung, and when overexpressed with TRPM2-L, protected cells from apoptosis. Expression in malignant tissue is thought to result from hypomethylation of a specific CpG island in the TRPM2 C-terminus. Little is known about mechanisms which control differential splicing of TRPM2 isoforms, but the ratio of isoform expression may have an important impact on susceptibility to oxidative stress.

TRPM2 enhances susceptibility to oxidative stress-induced cell death in a number of cell types [33, 34, 53, 60, 62]. In heterologous expression systems, exposure to oxidative stress enhances Ca^{2+} influx and cell death in cells expressing TRPM2-L [33, 47, 52]. Inhibition of endogenous TRPM2 function by expression of the dominant negative TRPM2-S, down regulation of TRPM2-L with RNA interference, or

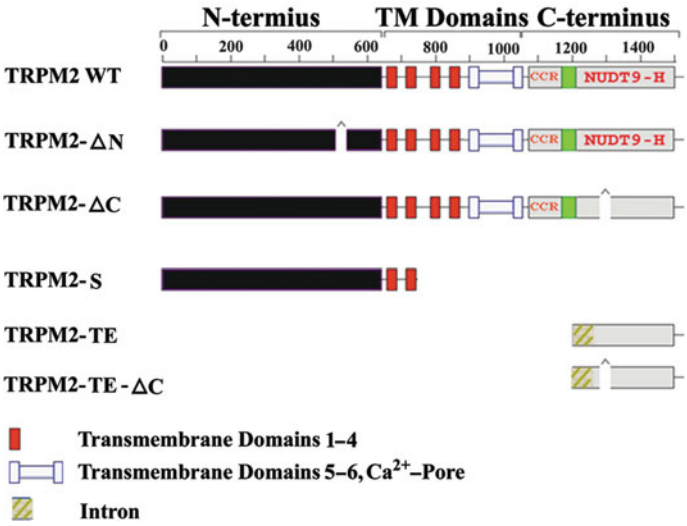

Fig. 29.2 Schematic representation of TRPM2 isoforms. Membrane spanning domains 1–4 and the putative pore region including transmembrane domains 5–6 are indicated. CCR represents the coiled coil region which may mediate protein/protein interactions. NUDT9-H represents the NUDT9 ADP-ribose hydrolase domain. TRPM2-△N has a deletion of aa 538–557 in the N-terminus. TRPM2-△C has a deletion of aa 1292–1325 in the C-terminus. TRPM2-S is missing four of six transmembrane domains and the putative calcium pore. TRPM2-TE consists of a short 22–24 kDa C-terminal fragment resulting from hypomethylation of a specific CpG island. TRPM2-TE-ΔC is a 184 amino acid, 21 kDa protein which differs from TRPM2-TE by a deletion of aa 1292–1325, also absent in TRPM2-△C

calcium chelation all blocked the rise in $[Ca^{2+}]_i$ induced by oxidative stress and protected cells from apoptosis [33, 34, 62].

Because of its broad expression profile, TRPM2 can modulate oxidative stress in a number of different tissues including brain, the cardiovascular system, and lymphocytes. The striatum has been shown to be highly vulnerable to ischemia/reperfusion injury [65]. TRPM2 is involved in oxidant injury to striatal cells. It may also be involved in the pathogenesis of Alzheimer's disease through activation by amyloid β-peptide, a main component of senile plaques which causes neuronal injury through generation of oxidative stress. In primary cultures of rat striatal cells which express TRPM2 endogenously, H_2O_2 or amyloid β-peptide induced an increase in $[Ca^{2+}]_i$ and cell death, which was inhibited by expression of TRPM2-S or by reduction in endogenous TRPM2 levels by RNA interference [46]. A TRPM2 variant (TRPM2P1018L) with enhanced inactivation has been identified in Guamanian amyotrophic lateral sclerosis and parkinsonism-dementia [66]. TRPM2 channels have been found to play an important role in the apoptotic component of ischemia/reperfusion injury in cardiomyocytes by inducing mitochondrial sodium and calcium overload, leading to mitochondrial membrane disruption, cytochrome c release, caspase-3 dependent chromatin condensation and myocyte

death [67]. Necrotic changes were also observed which were caspase-3 independent but PARP-dependent. Inhibition of both TRPM2 and PARP totally abolished H_2O_2-induced myocyte death [67]. ROS are important regulators of the vascular barrier. H_2O_2 induces an increase in endothelial permeability through TRPM2 activated Ca^{2+} entry [68, 69]. In a concentration-dependent manner, H_2O_2 decreased transmonolayer transendothelial electrical resistance, indicating opening of interendothelial junctions. Overexpression of TRPM2-L enhanced H_2O_2-mediated Ca^{2+} entry, cationic current, and the transendothelial electrical resistance decrease, whereas these were inhibited by TRPM2 depletion with siRNA, overexpression of the dominant negative TRPM2-S, or inhibition of ADPR formation. TRPM2 may be an important target to protect against oxidant-induced endothelial barrier disruption in a number of disease processes including acute respiratory distress syndrome and ischemia/reperfusion injury [68, 69].

TRPM2 channels are widely expressed in the immune system and play an important role in immune responses to oxidative stress. CD38 is a transmembrane glycoprotein, expressed in many tissues including lymphoid and myeloid cells, which use β-NAD^+ to produce ADPR, cADPR, and nicotinic acid adenine dinucleotide phosphate ($NAADP^+$) [70]. Through TRPM2, ADPR acting in synergy with cADPR and NAADP may play a major role in CD38-dependent Ca^{2+} influx, signaling in immune cells, and cell migration in phagocytes [71, 72]. A complex issue is whether CD38 is involved in regulation of intracellular ADPR levels, since the enzymatic activity of CD38 is extracellular. ROS levels in cells increase during infection following production by neutrophils and phagocytes, or in response to environmental factors including ionizing radiation or cytotoxic drugs. Oxidants are then thought to activate PARP/PARG, resulting in production of ADPR, modulating TRPM2 opening and activating the downstream cascade. Drugs interfering with this pathway may have a potent effect on modifying the immune response.

TRPM2 is also of functional importance in diabetes through its ability to regulate oxidant-induced beta cell death [73]. Inhibition of TRPM2 function may be an important and broad approach to protect cells from death following oxidant stress. This strategy could protect a range of tissues including heart and brain from oxidative stress-induced cell death following ischemia/reperfusion injury, as well as other tissues from less acute injury associated with oxidant stress including bone marrow, pancreas, and brain (Alzheimer's). Understanding how expression of TRPM2 isoforms and channel activation are regulated is an important area of research which may result in novel approaches to modulate cell viability.

29.3.2 TRPM7

TRPM7 is a widely expressed member of the TRPM ion channel subfamily. It has a C-terminal serine/threonine kinase domain with homology to the eEF2 α-kinase family [74, 75]. TRPM7 is a divalent cation channel which is permeable to Mg^{2+}, a rare feature among ion channels [74]. TRPM7 currents are inhibited by Mg^{2+} and Zn^{2+}, and activated by low levels of MgADP. TRPM6 and TRPM7 are two ion channels involved in regulation of cellular Mg^{2+} homeostasis [76, 77].

TRPM7 has been shown to be involved in cell proliferation and cell cycle progression. Reactive oxygen/nitrogen species can activate cation conductance through TRPM7, contributing to anoxic neuronal death. Overexpression of TRPM7 in HEK cells resulted in cell swelling, detachment, and death in 48–72 h [36, 74], whereas suppression of TRPM7 expression in primary cortical neurons blocked TRPM7 currents, Ca^{2+} influx, and reactive oxygen species production, protecting cells from anoxic cell death [36]. On the other hand, targeted deletion of TRPM7 in DT-40 B was lethal. These cells exhibited Mg^{2+} deficiency, growth arrest, and death within 24 h unless rescued by increased levels of extracellular Mg^{2+} [74]. These studies, along with others in which TRPM7 expression was down regulated [78, 79], demonstrate that precise regulation of TRPM7 expression is necessary for cell survival. However, siRNA targeted to TRPM7 also reduced TRPM2 levels [36], suggesting that expression of TRPM2 and TRPM7 are interdependent. This makes it difficult to definitively distinguish the roles of TRPM2 and TRPM7 in anoxic injury. Recently, no significant evidence was found for an association between TRPM7 genetic variants and type 2 diabetes [80] or risk for ischemic stroke [81], but the single nucleotide polymorphisms studied may not have captured all of the important genetic variability in TRPM7.

29.4 TRPV in Oxidative Stress

The TRPV subfamily of TRP proteins was named because the first member, TRPV1, is activated by the inflammatory vanilloid compound capsaicin which gives spicy foods their characteristic taste. TRPV family members are involved in osmosensation, thermosensation, mechanosensation, and chemosensation [4, 5]. TRPV1 is a calcium permeable, nonselective cation channel which is gated by a number of stimuli including heat, low pH, capsaicin, and other endogenous ligands. TRPV1 can act as a signal integrator in response to multiple harmful stimuli. Repeated activation of TRPV1 has previously been shown to result in increased $[Ca^{2+}]_i$, oxidative stress, and apoptotic cell injury [82, 83]. Recently, TRPV1 activation by capsaicin was found to increase substantially following oxidative stress [84]. The sensitization is long standing, overrides receptor desensitization, and involves covalent modification of conserved cysteines [84]. Oxidation represents an independent pathway from phosphorylation, desensitization, and acidic extracellular pH, acting to increase the gain of TRPV1 [84]. Through this mechanism, oxidative stress may mediate TRPV1 responses including pain sensation during inflammation or tissue injury.

The TRPV1 channel is involved in two aspects of the pathogenesis of diabetes. TRPV1 has been shown to play a role in diabetes through its role in pancreatic beta cell death [85]. TRPV1 is also highly expressed in large sensory dorsal root ganglion (DRG) neurons. Capsaicin induced increased oxidative stress as well as cytosolic cytochrome c and activation of caspase-3 in DRG neurons isolated from diabetic rats [86]. Treatment with capsazepine, a competitive TRPV1 antagonist, markedly reduced these changes in response to capsaicin, and prevented cell injury in large DRG neurons in diabetic rats in vivo. These data suggest that increased expression

and activation of TRPV1 in large DRG neurons are associated with oxidative stress and neuronal injury in early diabetic sensory neuropathy [86].

TRPC1, TRPC4, TRPV1, and TRPV4 all play an important role in endothelium-dependent vasorelaxation [8]. In addition, the TRP channels TRPC1, TRPC4, TRPV1, and TRPV4 can act as NO sensors in endothelial cells [31]. This data suggests that these channels could play an important role in diseases involving endothelial dysfunction mediated by oxidative stress.

29.5 Future Perspectives

Members of the TRP channel superfamily, particularly TRPM2, are now recognized to play important roles in oxidant stress-induced cell injury. In some cases, this is secondary to widespread tissue expression of channels which are activated indirectly by increases in oxygen or nitrogen free radicals. In certain tissues, channel expression contributes to oxidative injury through more specific activation pathways. In the near future, it is likely that additional TRP channels will be identified which contribute to oxidant injury, and the mechanisms through which they are regulated and mediate their downstream effects will be better defined. Ultimately, therapeutic approaches which modulate activation of TRP channels by oxidant stress may significantly reduce tissue damage in a number of disease processes including those resulting from ischemic injury or diabetes. Since the role of oxidant stress in malignant cell growth and chemotherapy response is increasingly recognized, TRP channel modulation may also be utilized in future targeted therapies in cancer.

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