TRPM2

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Contents

Abstract

TRPM2 is the second member of the transient receptor potential melastatin-related (TRPM) family of cation channels. The protein is widely expressed including in the brain, immune system, endocrine cells, and endothelia. It embodies both ion channel functionality and enzymatic ADP-ribose (ADPr) hydrolase activity. TRPM2 is a Ca^{2+}-permeable nonselective cation channel embedded in the plasma membrane and/or lysosomal compartments that is primarily activated in a synergistic fashion by intracellular ADP-ribose (ADPr) and Ca^{2+}. It is also activated by reactive oxygen and nitrogen species (ROS/NOS) and enhanced by additional factors, such as cyclic ADPr and NAADP, while inhibited by permeating protons (acidic pH) and adenosine monophosphate (AMP). Activation of TRPM2 leads to increases in intracellular Ca^{2+} levels, which can serve signaling roles in inflammatory and secretory cells

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through release of vesicular mediators (e.g., cytokines, neurotransmitters, insulin) and in extreme cases can induce apoptotic and necrotic cell death under oxidative stress.

Keywords
Calcium • Non-selective cation • Transient receptor potential channel • Reactive oxygen species • ADP ribose • Nucleoside diphosphate hydrolase • Inflammation • Apoptosis • Cancer • Diabetes

1 Gene

TRPM2 was first isolated from human brain in 1998 and given the designation TRPC7 (transient receptor potential-related channel 7) (Nagamine et al. 1998). The protein was later categorized more appropriately as a member of the long TRPC subfamily nomenclature and referred to as LTRPC2 (Harteneck et al. 2000). In 2002, a unified nomenclature assigned it to the melastatin subfamily of TRP channels as TRPM2 (Montell et al. 2002).

The gene coding human TRPM2 is located between two markers D21S400 and D21S171 on human chromosome 21q22.3 and consists of 32 exons spanning 90 kb and mapping a 1503 amino acid long protein (Nagamine et al. 1998). An additional exon has been reported (Uemura et al. 2005), indicating two transcription start sites in the human TRPM2 gene that yield two forms of TRPM2: a 6.5 kb transcript encoding the 1503 amino acid full-length long form TRPM2 (TRPM2-L) that is widely expressed and starts from a noncoding exon associated with a CpG island, and a shorter 5.5 kb transcript that starts from intron 4 and encodes a 1289 amino acid striatum short form TRPM2 (TRPM2-SSF) that lacks N-terminal 214 amino acid residues of the long form. In addition, various TRPM2 splice variants have been identified: TRPM2-ΔN, TRPM2-ΔC, TRPM2-ΔNΔC, and TRPM2-S (see Sect. 3 for specifics). A recent study found that 17β-estradiol (E2) treatment induces an increase in TRPM2 transcripts in human endometrial cells and identified a functional estrogen response element (ERE) in the 3′-untranslated region (UTR) of the TRPM2 gene (Hiroi et al. 2013a).

The mouse Trpm2 gene contains 34 exons and spans about 61 kb. In contrast to the human gene, it has only one transcription start site and no second promoter to produce a shorter mRNA. The mouse gene also does not exhibit any predicted CpG islands (Uemura et al. 2005).

2 Expression

TRPM2 is widely expressed in the central nervous system (CNS), including hippocampus, thalamus, striatum, and cerebral cortex, as well as in microglia (Nagamine et al. 1998; Kraft et al. 2004; Fonfria et al. 2005, 2006a, b; Lipski et al. 2006; Olah

et al. 2009; Roedding et al. 2013). However, its presence at mRNA and/or protein levels is not ubiquitous throughout all CNS regions and within all neuronal subtypes. Indeed, TRPM2 could not be detected within either cultured astrocytes or granule cells of the cerebellum (Kraft et al. 2004). Additionally, while hippocampal CA1 pyramidal neurons possess functional TRPM2 channels (Olah et al. 2009; Belrose et al. 2012), hippocampal CA1 stratum radiatum interneurons show no functional evidence of TRPM2 expression (Olah et al. 2009).

TRPM2 is also detected in other tissues such as the bone marrow, spleen, heart, liver, lung, placenta endometrium, and gastrointestinal tract and in different cell types like pancreatic β-cells (Fonfria et al. 2006b; Togashi et al. 2006; Ishii et al. 2006a, b; Lange et al. 2009; Uchida and Tominaga 2011; Uchida et al. 2011; Hiroi et al. 2013a), salivary gland (Liu et al. 2013), endothelial cells (Hecquet et al. 2008, 2010; Hecquet and Malik 2009; Sun et al. 2012), heart and vasculature (Yang et al. 2006; Takahashi et al. 2012; Miller et al. 2013), and immune cells (neutrophils, megakaryocytes, monocytes, macrophages, B lymphoblast cells, T lymphocytes, and mast cells) (Heiner et al. 2003a, b; Carter et al. 2006; Yamamoto et al. 2008; Lange et al. 2008; Wenning et al. 2011; Roedding et al. 2012; Kashio et al. 2012; Magnone et al. 2012; Oda et al. 2013; Hiroi et al. 2013b; Knowles et al. 2013).

Although originally described as a plasma membrane channel, TRPM2 has been found to also function as a lysosomal Ca^{2+} release channel in pancreatic β-cells and dendritic cells (Lange et al. 2009; Sumoza-Toledo et al. 2011). It shares this cellular localization in the endosomal pathway with the mucolipin channels TRPML1–3 (Piper and Luzio 2004; Dong et al. 2010; Cheng et al. 2010) and the two-pore channels TPC1–3 (Calcraft et al. 2009; Brailoiu et al. 2009; Galione et al. 2009; Zong et al. 2009; Ruas et al. 2010; Pitt et al. 2010). Intracellular localization, albeit not in lysosomes, has also been reported for other TRP channels, including TRPV1 (Morenilla-Palao et al. 2004), TRPC5 (Bezzerides et al. 2004), TRPC3 (Singh et al. 2004), TRPM8 (Thebault et al. 2005), and TRPM7 (Oancea et al. 2006). The factors that would determine the cellular localization of TRPM2 and various other TRP channels remain to be defined, as well as whether the cellular localization serves a particular cellular function.

3 The Channel Protein Including Structural Aspects

The full-length TRPM2 consists of an intracellular N terminus of ~700 amino acids, the TRPM homology region, followed by a region of approximately 300 amino acids (residues 762–1048) containing six putative transmembrane domains (S1–S6), a pore-forming loop domain located between S5 and S6, an approximately 100 amino acid region of high coiled-coil character (CCR), a short 30 amino acid linker region, and a unique intracellular C-terminal adenosine diphosphate ribose (ADPr) pyrophosphatase domain (residues 1236–1503, Nudix-like or NUDT9 homology domain) (Fig. 1) (Perraud et al. 2001, 2003a; Sano et al. 2001; Fleig and Penner 2004a, b).

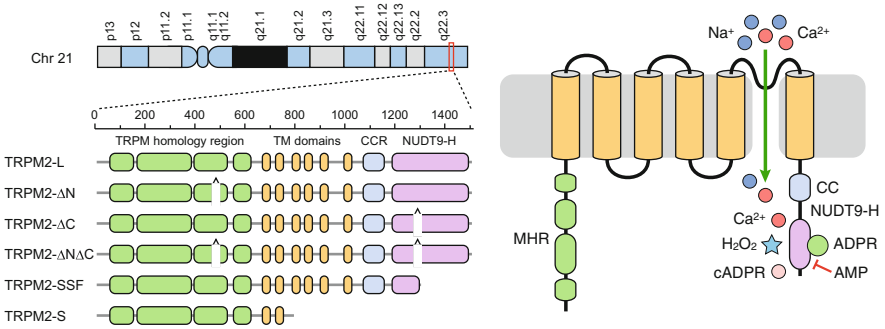

Fig. 1 Schematic of TRPM2 gene and encoded protein isoforms (*left*) and membrane topology (*right*). The human chromosome 21 schematic (*top left*) shows the location of TRPM2 gene in the sub-band 3 of band 2 of the second region of the long arm q of the chromosome 21 (21q22.3). The gene encodes a full-length TRPM2 form (TRPM2-L) and various splice variants (*bottom left*). The full-length protein is composed of 1503 amino acids (1507 in mouse and rat). Segments in the N terminus denote the four domains of the TRPM homology region (MHR), followed by six transmembrane segments (TM: S1–S6) with the putative pore-forming region (S5–S6). The C-terminal region contains a coiled-coil region (CCR) and a NUDT9-homology region (NUDT9-H). The caret (^) denotes the deletions within the N- and C-terminal domains of TRPM2 variants. The membrane topology of TRPM2 (*right*) shows that both N- and C-termini are in the cytosol. ADP-ribose (ADPr) binds to the NUDT9-H region to induce channel gating and enable calcium (Ca^{2+}) and sodium (Na^{+}) influx. The NUDT9-H enzymatic activity hydrolyses ADPr to ribose 5-phosphate and adenosine monophosphate (AMP). AMP, in turn, acts as a negative regulator of TRPM2. TRPM2 gating by ADPr is facilitated by hydrogen (H_2O_2), cyclic ADPr (cADPr), and Ca^{2+}

The TRPM2 N terminus has four homologous domains and a calmodulin (CaM)-binding IQ-like motif located at 406–416AA, which plays a role in modulating channel activation (Perraud et al. 2001; Sano et al. 2001; McHugh et al. 2003; Fleig and Penner 2004a, b; Tong et al. 2006). It was also reported that deletion of a stretch of 20 amino acid residues (Δ537–556) in the N terminus, corresponding to the TRPM2-ΔN splice variant in neutrophils, abolishes any channel function (Wehage et al. 2002). This dysfunction is believed to be related to undetermined motifs within the ΔN-stretch, but not the IQ-like motif, and two SH3-binding (PxxP) motifs found in this region (Kühn et al. 2009). Unlike their close relatives in the TRPC and TRPV subfamilies, TRPM channels contain a pair of cysteine residues in the pore region (positions 996 and 1008 for TRPM2), whose substitutions with either alanine or serine did not affect protein expression/trafficking or localization, but generated TRPM2 channels that were functionally unresponsive to ADPr (Mei et al. 2006a). Furthermore, a substitution mutation of I1045K on the distal part of the S6 domain was crucial for the selectivity of TRPM2, transforming TRPM2 from a cation to an anion channel (Kühn et al. 2007).

The CCR region is hypothesized to be involved in several important functions, including protein trafficking, channel tetrameric assembly, and gating (Perraud et al. 2003a; Jiang 2007). CCR deletion or site-directed mutagenesis did not affect protein expression, but resulted in severe disruption of the TRPM2 subunit

assemblies and substantial loss of ADPr-evoked channel currents (Mei et al. 2006b). This was due to reduced trafficking of TRPM2 subunits and proper localization at the membrane level.

The NUDT9-H region that gives TRPM2 the chanzyme designation is named after the mitochondrial ADP-ribose pyrophosphatase NUDT9 with whom it shares 39 % homology (Shen et al. 2003). The NUDT9-H region contains a Nudix box sequence motif G*X*(5)E*X*(7)REU*X*EE*X*U (*X* represents any amino acid residue, and U represents a large hydrophobic residue) that is characteristic of a family of diverse pyrophosphatases that accept nucleoside diphosphate substrates like ADPr (Kühn and Lückhoff 2004; Mildvan et al. 2005). Biochemical analyses have indicated that NUDT9 consists of two domains, a C-terminal CORE domain containing the structures required for ADPrase activity and an N-terminal CAP domain which enhances the CORE domain's affinity for ADPr (Perraud et al. 2003a). Deletion of the NUDT9-H domain strongly decreases TRPM2 plasma membrane expression, indicating its vital role for normal channel assembly and surface trafficking (Perraud et al. 2005). This role has been specifically linked to the NUDT9-H CORE domain, since the TRPM2-ΔC channels that lack amino acids in the NUDT9-H CAP region are properly expressed at the cell surface (Perraud et al. 2003a). Additionally, the NUDT9-H region is directly involved in TRPM2 channel gating by virtue of binding ADPr at multiple sites (Perraud et al. 2001, 2003a; Kühn and Lückhoff 2004). It appears that the binding of ADPr rather than enzymatic activity of TRPM2's NUDT9-H domain is critical for channel gating, as mutations that eliminate ADPrase activity retain channel gating capacity (Perraud et al. 2003b, 2005). Three-dimensional reconstruction of purified tetrameric TRPM2 using transmission electron microscopy has yielded first insights into the structure of the channel protein at 2.8 nm resolution, revealing a swollen, bell-shaped structure of 18 nm in width and 25 nm in height (Maruyama et al. 2007).

In addition to the full-length TRPM2 (TRPM2-L), physiological TRPM2 splice variants missing one or both exons 11 and 27 (Fig. 1) have been identified in human hematopoietic cells (HL-60 monocytes and neutrophil granulocytes): TRPM2-ΔN is characterized by a deletion in the N terminus (residues K538-Q557), TRPM2-ΔC lacks residues in the C terminus (T1292–L1325), and TRPM2-ΔNΔC carries both deletions (Wehage et al. 2002). An additional short variant, TRPM2-S, contains only the N terminus and the first two transmembrane segments and is generated by an additional stop codon (TAG) at the splice junction between exons 16 and 17 (Fig. 1). This variant has been found in the bone marrow, brain and pulmonary arteries, and aorta (Zhang et al. 2003; Yang et al. 2006; Vázquez and Valverde 2006; Hecquet and Malik 2009) and may act as a dominant negative inhibitor of TRPM2 activity (Zhang et al. 2003). The TRPM2-ΔC proteins encoded by exon 27 deletion transcripts carry a deletion within the NUDT9-H. While TRPM2-ΔN fails to respond to either ADPr or H_2O_2, it has been reported that the TRPM2-ΔC variant responds to H_2O_2 but not to ADPr, indicating a possible direct activation of TRPM2 by H_2O_2 (Wehage et al. 2002).

4 Interacting Proteins

Only a few studies have investigated TRPM2 channel interaction with other proteins (So et al.). It has been reported that the TRPM2-S isoform acts as a suppressor of H_2O_2-induced calcium influx through the full-length TRPM2 (TRPM2-L) channels when heterologously expressed in HEK-293T cells. This effect involves a direct interaction between the two isoforms and not a modification in subcellular localization of TRPM2-L (Zhang et al. 2003). A study examining the TRPM2 protein partners that regulate cell survival has found that the protein tyrosine phosphatase-L1 (PTPL1) interacts with TRPM2 channels to decrease their tyrosine phosphorylation and activity and thereby reduce H_2O_2- and TNF-α-induced cell death in HEK-293 cells (Zhang et al. 2007). This interaction was examined and confirmed endogenously in the human monocytic U937-ecoR cells, supporting the relevance of TRPM2 in the cell-death resistance phenotype within the PTPL1-overexpressing tumors. Furthermore, immunoprecipitation analysis has demonstrated physical interaction of the N- and C-terminal cytoplasmic tails of TRPM2 with the EF-hand domain-containing protein 1 (EFHC1), whose mutation causes juvenile myoclonic epilepsy (JME) via mechanisms including neuronal apoptosis (Katano et al. 2012). This study also reported that this interaction significantly potentiated cell death mediated by H_2O_2, ADPr-induced Ca^{2+} responses, and cationic currents via recombinant TRPM2 in HEK-293 cells.

An important functional interaction is provided by the calcium sensor calmodulin (CaM). Its involvement in TRPM2 modulation appears to be responsible, at least in part, for the Ca^{2+}-dependent activation of TRPM2 (Tong et al. 2006). Thus, overexpression of a dominant negative mutant of CaM was able to compete with endogenous CaM and inhibit TRPM2-mediated increases in $[Ca^{2+}]_i$ and immunoprecipitation confirmed a direct interaction between CaM and TRPM2. A strong CaM binding region was identified in the TRPM2 N terminus (amino acids 1–730) and weak binding region in the C terminus (amino acids 1060–1503). CaM is believed to bind to an IQ-like consensus binding motif on the TRPM2 N terminus (amino acids 406–416) since a substitution mutant of this motif (TRPM2-IQMUT1) reduced the CaM-TRPM2 binding (Tong et al. 2006). The IQ-like motif was shown to be the mechanism mediating Ca^{2+}-activated TRPM2 currents (Du et al. 2009a). Additionally, intracellular perfusion of cells with CaM in the patch pipette significantly increased ADPr-activated TRPM2 currents, whereas exposure to 2 μM calmidazolium, a known CaM antagonist, prevented ADPr-mediated TRPM2 currents (Starkus et al. 2007).

One study has found that the ΔC splice variant of TRPM2 co-immunoprecipitates with CD38 in HeLa cells and the authors proposed that this close interaction may form the basis for hypertonicity-induced gating of this splice variant (Numata et al. 2012).

Finally, proteome-wide site-specific quantifications of endogenous putative ubiquitylation sites indicate posttranslational modifications of TRPM2 (Wagner et al. 2011; Kim et al. 2011), although their physiological context and functional consequences remain to be explored.

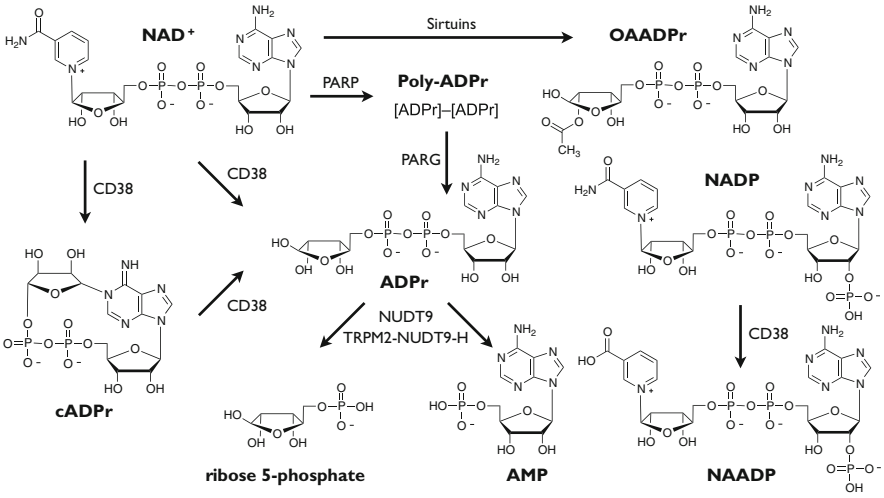

Fig. 2 Schematic of metabolic pathways of pyridine nucleotides acting on TRPM2. The primary activator of TRPM2 is ADP-ribose (ADPr), which can be produced from several sources through various enzymatic reactions. Nicotinamide adenine dinucleotide (NAD^+) can be directly converted to ADPr by CD38 NADase activity or indirectly through the intermediate cyclic ADPr (cADPr)—a facilitator of ADPr-mediated activation of TRPM2—that is produced by CD38's ADP-ribosyl cyclase activity and can further be converted to ADPr via cADPr hydrolase activity of CD38. NAD^+ is also the substrate of poly(ADPr) polymerase (PARP), which creates ADPr polymers that can be hydrolyzed to free ADPr by the poly(ADPr) glycohydrolase (PARG) and sirtuins, which generate the TRPM2 agonist 2′-*O*-acetyl-ADPr (OAADPr). ADPr itself is the substrate of the ADPr pyrophosphatase NUDT9 as well TRPM2's endogenous NUDT9 homology domain in the N terminus, yielding the inactive metabolite ribose 6-phosphate and the TRPM2 inhibitor adenosine monophosphate (AMP). Finally, it is thought that NAADP, another facilitator of ADPr-mediated TRPM2 gating, can be formed from NADP by a base-exchange reaction via CD38

5 A Biophysical Description of the Channel Function, Permeation, and Gating

TRPM2 is a homo-tetrameric nonselective cation permeable channel that exhibits a perfectly linear I/V curve (Perraud et al. 2003a; Csanády and Törocsik 2009). The channel activates in response to low micromolar levels of cytosolic ADPr with half-maximal effective concentrations (EC_{50}) of 1–90 μM (Perraud et al. 2001; Sano et al. 2001; Inamura et al. 2003; Beck et al. 2006; Gasser et al. 2006; Starkus et al. 2007; Lange et al. 2008). The variability in EC_{50} values may arise from the modulatory mechanisms expressed in a given cell type. At the cellular level, free ADPr is mainly produced by the hydrolysis of NAD^+ and/or cADPr by glycohydrolases, including the ectoenzymes CD38 and CD157, as well as the mitochondrial NADase (Lund et al. 1995, 1998; Lund 2006; Malavasi et al. 2006). A further source of ADPr is provided by the combined action of poly

(ADPr) polymerases (PARP) and poly(ADPr) glycohydrolases (PARG), which indirectly generate ADPr via formation and hydrolysis of poly-ADPr when hyperactivated in response to DNA damage (Esposito and Cuzzocrea 2009; Caiafa et al. 2009; Fauzee et al. 2010). Figure 2 illustrates the various adenine nucleotides and their metabolic pathways.

The ability of other adenine nucleotide second messengers, metabolically related to ADPr, to activate TRPM2 channels has been described. These include cyclic ADPr (cADPr; EC_{50} ~0.7 mM) (Kolisek et al. 2005; Lange et al. 2008) and nicotinic acid adenine dinucleotide phosphate (NAADP; EC_{50} ~0.73 mM) (Beck et al. 2006; Lange et al. 2008). Even though activation of TRPM2 by high concentrations of nicotinamide adenine dinucleotide (NAD^+; EC_{50} ~1–1.8 mM) has been observed (Sano et al. 2001; Hara et al. 2002; Naziroğlu and Lückhoff 2008), its status as a direct agonist for TRPM2 remains uncertain, since at least in some studies, contaminations with ADPr or metabolism of NAD^+ may account for the observed TRPM2 activation (Beck et al. 2006; Grubisha et al. 2006). The relatively high concentrations of cADPr and NAADP required to activate TRPM2 directly are above physiological levels; however, these adenine nucleotide second messengers can synergize with ADPr and increase TRPM2 sensitivity at much lower doses. In fact, it has been reported that 10 μM of cADPr may facilitate TRPM2 function such that nanomolar (possibly ambient) cytosolic levels of ADPr can activate the channel (Kolisek et al. 2005). Whether these nucleotides bind directly to the Nudix domain, or to different cooperative sites, or are converted to ADPr is not clearly understood.

A significant enzymatic source of ADPr is CD38, a multifunctional ectoenzyme that is widely expressed in hematopoietic and non-hematopoietic cells. It uses NAD^+ as a substrate to catalyze the production of ADPr, cADPr, and NAADP (Lund et al. 1995, 1998). In neutrophils both CD38 and TRPM2 channels are present in the plasma membrane, possibly establishing a signaling pathway that involves CD38, ADPr production, and TRPM2 activation. Indeed, CD38 knockout (KO) neutrophils stimulated with the bacterial peptide formyl-methionyl-leucyl-phenylalanine (fMLP) show a reduced Ca^{2+} response when compared to wild-type cells (Partida-Sánchez et al. 2003). Similarly, fMLP-treated TRPM2 KO neutrophils have defects in Ca^{2+} influx (Yamamoto et al. 2008). Additionally, the fMLP-induced Ca^{2+} entry in neutrophils is inhibited with the ADPr and cADPr antagonists 8Br-ADPr and 8Br-cADPr, respectively (Partida-Sánchez et al. 2004, 2007). Although ADPr is the main product of CD38 and evidence points to TRPM2 as a mediator of Ca^{2+} entry, there are still open questions such as to whether and how the extracellular ADPr generated by CD38 crosses the plasma membrane and acts on the cytosolic Nudix domain of TRPM2 channels (Franco et al. 1998; Bruzzone et al. 2001). A further metabolite coupling to TRPM2 is the sirtuin-generated acetyl-ADP-ribose product 2′-*O*-acetyl-ADP-ribose (OAADPr), which also induces TRPM2 currents by direct binding to the Nudix domain with an EC_{50} of ~100 μM (Grubisha et al. 2006; Tong and Denu 2010). OAADPr is produced by a histone/protein deacetylase reaction mediated by a family of silent information regulator 2 (Sir2 or sirtuin)-related NAD-dependent protein deacetylases. Indeed,

the mammalian sirtuins SIRT2 and SIRT3 have been suggested to generate the OAADPr that leads to TRPM2-dependent cell death induced by puromycin, while specific RNAi knockdown in TRPM2-expressing cells protects these cells from cell death (Grubisha et al. 2006).

The gating and full activation of TRPM2 channels by ADPr is highly sensitive to Ca^{2+}, as either absence of external Ca^{2+} or strong buffering of internal Ca^{2+} to low levels (<30 nM) substantially inhibit gating of TRPM2 channels by ADPr (McHugh et al. 2003; Starkus et al. 2007; Csanády and Törocsik 2009). This Ca^{2+} effect is not mimicked by other divalent cations such as Mg^{2+}, Ba^{2+}, or Zn^{2+} (Starkus et al. 2007). Moreover, 200 μM external Ca^{2+} is sufficient and as efficient as 1 mM Ca^{2+} in promoting TRPM2 activation (Starkus et al. 2007). It has also been suggested that Ca^{2+} may gate the channel directly in a dose-dependent manner with an EC_{50} of 17 μM (Du et al. 2009a), possibly as a result of conformational changes due to Ca^{2+}-dependent binding of CaM with the TRPM2 IQ-like motif or other intracellular sites (Du et al. 2009a). However, other groups have not observed Ca^{2+}-induced activation in the absence of ADPr (McHugh et al. 2003; Starkus et al. 2007; Csanády and Törocsik 2009), and it is therefore possible that TRPM2 activation is secondary to ADPr production or ADPr release from mitochondria caused by high Ca^{2+} concentrations. Similarly to the facilitating role of intracellular Ca^{2+}, it has been suggested that intracellular chloride ions may also provide a facilitating effect on ADPr- and H_2O_2-induced activation of TRPM2, promoting ADPr/Ca^{2+}-induced TRPM2 gating with an EC_{50} of ~18 mM (Hong et al. 2010). This effect has been attributed to a critical lysine residue K1110 that is located between TRPM2's transmembrane domains and the coiled-coil region and whose mutation inhibited channel activation by both ADPr and H_2O_2 (Kim et al. 2013).

TRPM2 channels can also be activated by micromolar levels of H_2O_2 and agents that produce reactive oxygen/nitrogen species, providing a direct link to inflammation, oxidative stress, and cell death (Hara et al. 2002; Kolisek et al. 2005; Ishii et al. 2006b; Yamamoto et al. 2008; Takahashi et al. 2011; Haraguchi et al. 2012). Whether or not H_2O_2 can gate TRPM2 directly and independently of ADPr remains unclear. Wehage et al. found that TRPM2-ΔC channels expressed in HEK293 cells, which fail to respond to ADPr, could still be activated by H_2O_2, suggesting distinct and independent gating mechanisms of ADPr and H_2O_2 (Wehage et al. 2002). However, a later study in Chinese Hamster Ovary cells could not confirm direct H_2O_2 activation (Kühn and Lückhoff 2004). Kolisek et al. reported that H_2O_2 by itself, like cADPr, was not effective in activating TRPM2, but strongly facilitated ADPr-mediated gating. Hence, an alternative explanation for the capacity of H_2O_2 to induce TRPM2 activation may relate to its ability to both mobilize ADPr from mitochondria (Perraud et al. 2005) and, at the same time, synergize with ADPr in gating the channel (Kolisek et al. 2005). The notion that release of ADPr from mitochondria could be a critical mechanism leading to TRPM2 gating (Ayub and Hallett 2004) was confirmed by experiments showing that H_2O_2-induced TRMP2 currents were suppressed when reducing the ADPr concentration within the mitochondria (Perraud et al. 2005).

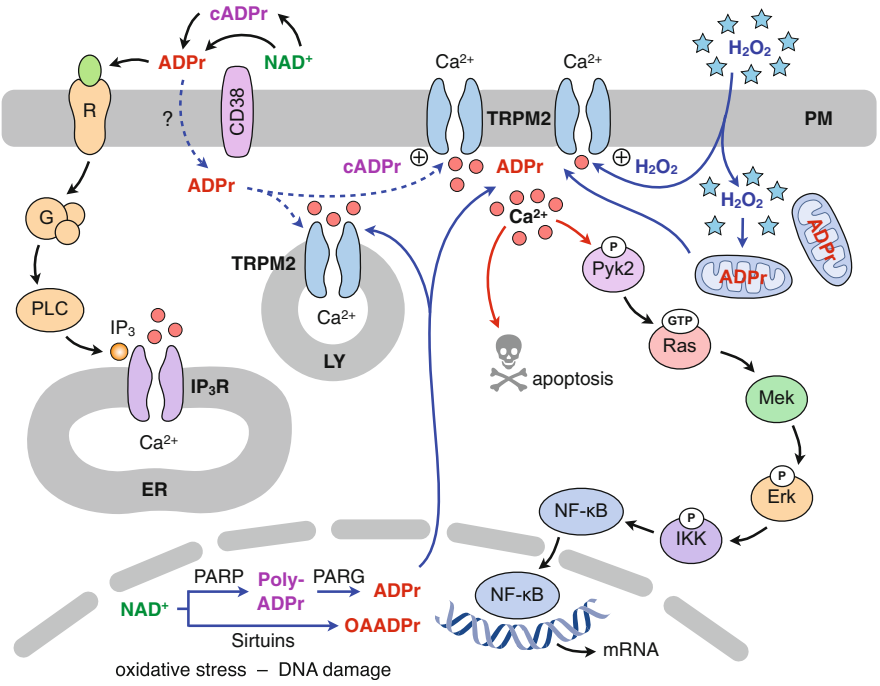

Fig. 3 Upstream and downstream signaling mechanisms for TRPM2 activation. External NAD^+ and reactive oxygen species (ROS), including H_2O_2, accumulate during inflammation and tissue damage. NAD^+ may be converted to ADPr and cADPr by the ectoenzyme CD38. Extracellular ADPr may then bind to G-protein-coupled purinergic receptors and increase $[Ca^{2+}]_i$ through Ca^{2+} release from stores via G-proteins and the phospholipase C (PLC) pathway with subsequent IP_3 production. ADPr may also translocate across the plasma membrane (PM) to gate TRPM2. H_2O_2 can also cross the plasma membrane and mobilize ADPr from mitochondria and both H_2O_2 and cADPr can synergize with ADPr to activate TRPM2. Additionally, ADPr is also generated from NAD^+ via poly-ADPr during ROS-induced DNA damage through activation of the PARP/PARG pathway. NAD^+ can also be used to generate *O*-acetyl-ADPr, another agonist of TRPM2, through nuclear and cytosolic sirtuins. Free cytosolic ADPr or OAADPr can act on the NUDT9-H of both lysosomal and plasma membrane TRPM2 channels, enabling Ca^{2+} influx across the plasma membrane and/or release of lysosomal Ca^{2+}, raising the Ca^{2+} concentration in the cytosol. Intracellular Ca^{2+} increases will activate different physiological processes including gene expression through Ca^{2+}-dependent signaling pathways such as MAP Kinase and NF-κB. Ca^{2+} overload may also trigger programmed cell death (apoptosis) and possibly necrosis

In addition to mitochondrial sources, ADPr may also be generated in the nucleus through the activation of the PARP/PARG pathway following oxidative stress and DNA damage (Fonfria et al. 2004). Poly(ADP-ribosyl)ation is regulated by the synthesizing enzyme poly(ADP-ribose) polymerase-1 (PARP-1) and the degrading enzyme poly(ADP-ribose) glycohydrolase (PARG) (Esposito and Cuzzocrea 2009; Caiafa et al. 2009; Fauzee et al. 2010), resulting in the production of free ADPr that can then activate TRPM2. The involvement of this mechanism has been demonstrated pharmacologically through the use of PARP inhibitors, which

effectively suppress H_2O_2-mediated and PARP-dependent Ca^{2+} increases through TRPM2 channels (Fonfria et al. 2004). Similarly, genetic PARP ablation in DT40 cells, which express TRPM2, results in loss of oxidative stress-induced Ca^{2+} responses normally seen in wild-type DT40 (Buelow et al. 2008). PARP-1 knockout mice have also implicated this enzyme, in combination with androgen receptor signaling, to be responsible for male-specific TRPM2 channel activation and neuronal injury (Shimizu et al. 2013). Figure 3 illustrates some of the most important signaling pathways for TRPM2 activation.

In pancreatic beta cells, the gating of TRPM2 appears to be influenced by temperature. It has been reported for rat insulinoma RIN-5F cells that temperatures higher than 35 °C can directly activate TRPM2 channels and potentiate ADPr- and cADPr-induced activation of TRPM2 (Togashi et al. 2006). A similar temperature-dependent potentiation of cADPr-induced Ca^{2+} signals via TRPM2 has been observed in NG108-15 neuronal cells (Amina et al. 2010). The underlying mechanisms and the possible physiological consequences of these effects remain to be identified.

A somewhat unusual activation mechanism has been proposed for the ΔC splice variant of TRPM2, which is insensitive to adenine nucleotides. Yet in HeLa cells, this variant has been suggested to function as a poorly Ca^{2+}-permeable cation channel that is activated by hypertonicity via nucleotide transport activity of CD38 (Numata et al. 2012).

In addition to the facilitating modulators of TRPM2 discussed above, the channel can also be inhibited. The first such negative regulator described was adenosine monophosphate (AMP) (Kolisek et al. 2005; Beck et al. 2006; Lange et al. 2009; Tóth and Csanády 2010), which represents a breakdown product of TRPM2's endogenous enzymatic domain, hydrolyzing the physiological agonist ADPr into AMP and ribose 5-phosphate (Perraud et al. 2001, 2003b). AMP can also be elevated as a result of ischemia and may attempt to limit Ca^{2+} entry through TRPM2. It remains to be determined whether the inhibitory effect of AMP is direct or indirectly mediated by AMP-dependent signals such as AMP kinase.

In addition to AMP, TRPM2 channels are negatively regulated by protons and cellular acidification (Du et al. 2009b; Starkus et al. 2010; Yang et al. 2010). Thus, TRPM2 currents are completely suppressed when cells are externally or internally exposed to pH of 5–6 (Du et al. 2009b; Starkus et al. 2010), although conflicting interpretations with respect to proton permeation through TRPM2 channels and the site of inhibitory action of protons have been presented. One study proposed that protons inhibit at the extracellular side (Du et al. 2009b), whereas two other laboratories suggest that the mechanism is linked to protons competing with Na^+ and Ca^{2+} ions for channel permeation, and channel closure results from a competitive antagonism of protons at an intracellular Ca^{2+}-binding site (Starkus et al. 2010; Csanády 2010).

Additional inhibition of TRPM2 currents has been observed with various divalent heavy metal cations, including Cu^{2+}, Hg^{2+}, Pb^{2+}, Fe^{2+}, Se^{2+} (Zeng et al. 2012), and Zn^{2+} (Yang et al. 2011). Of these ions, Cu^{2+}, Hg^{2+}, and Zn^{2+} are the most potent

and have been shown to act as extracellular pore-blocking antagonists (Yang et al. 2011; Zeng et al. 2012).

6 Physiological Functions in Native Cells, Organs, and Organ Systems

The TRPM2 expression profile throughout the body (Fonfria et al. 2006b) and the channel's role in Ca^{2+} mobilization from both extracellular and intracellular compartments makes it a strong candidate to mediate significant calcium-dependent physiological processes. The abundant presence of TRPM2 in the CNS has been investigated and related to some physiological functions, including TRPM2's contribution to synaptic transmission in hippocampal CA3-CA1 synapses and its activation following Ca^{2+} increases mediated by voltage-dependent Ca^{2+} channels and glutamate receptors (Olah et al. 2009; Xie et al. 2011). Additional roles for TRPM2 in the CNS are related to its presence in microglia, the host macrophages of the brain, where TRPM2 appears to be responsible for physiological microglia activation through ROS- and LPS-mediated signaling (Kraft et al. 2004; Fonfria et al. 2006a; Wehrhahn et al. 2010). However, the majority of studies place TRPM2 into the context of pathophysiological events of stroke/ischemia and neurodegeneration (Xie et al. 2011), where TRPM2's roles include numerous mechanisms that result in the promotion of cytokine release, the exacerbation of inflammation, and the initiation of neuronal death.

In addition to the neuronal and microglial populations of the CNS, TRPM2 is also localized in various cell types of the peripheral immune system, including neutrophils (Heiner et al. 2003a, b, 2006; Partida-Sanchez et al. 2007; Lange et al. 2008; Hiroi et al. 2013b), monocytes (Perraud et al. 2001; Yamamoto et al. 2008; Wehrhahn et al. 2010), macrophages (Kashio et al. 2012; Zou et al. 2013), dendritic cells (Partida-Sanchez et al. 2007; Sumoza-Toledo et al. 2011), and lymphocytes (Beck et al. 2006; Buelow et al. 2008; Roedding et al. 2012). In most cells, TRPM2 has been investigated in the context of inflammation, mediating responses to oxidative stress and/or chemoattractants, acting as a plasma membrane-resident mediator of stimulus-induced Ca^{2+} influx. Thus, Ca^{2+} influx through TRPM2 induced by H_2O_2 and ROS in monocytes, macrophages, and lymphocytes can directly mediate cytokine release and contribute to recruitment and activation of inflammatory cells to the site of injury (Sano et al. 2001; Yamamoto et al. 2009; Sumoza-Toledo et al. 2011; Kashio et al. 2012; Magnone et al. 2012; Oda et al. 2013; Knowles et al. 2013). Additionally, TRPM2-deficient mice show decreased levels of cytokines IL-12 and IFNγ and are more susceptible to infection with Listeria monocytogenes (Knowles et al. 2011). Interestingly, dendritic cells express TRPM2 exclusively intracellularly, where it acts as a lysosomal Ca^{2+} release channel and plays a role in cell maturation via chemokine production and cell migration (Sumoza-Toledo et al. 2011).

Paradoxically, TRPM2 has also been shown to inhibit ROS production in phagocytic cells and prevent endotoxin-induced lung inflammation

(Di et al. 2012). This has been linked to the dampening of NADPH oxidase-mediated ROS production through depolarization of the plasma membrane. As a result, TRPM2-KO mice exposed to endotoxin show enhanced inflammatory responses and reduced survival compared to WT mice.

Outside of the immune context, TRPM2 has also been identified in endocrine cells such as pancreatic β-cells (Qian et al. 2002; Togashi et al. 2006; Ishii et al. 2006a, b; Lange et al. 2009; Bari et al. 2009), where its activity has been demonstrated to contribute to glucose-induced insulin release and alloxan- and H_2O_2-mediated apoptosis (Herson and Ashford 1997, 1999; Togashi et al. 2006; Uchida and Tominaga 2011; Uchida et al. 2011). Uchida and collaborators have shown that glucose tolerance was impaired and insulin secretion was decreased in TRPM2 knockout mice. They also found that basal blood glucose levels were higher in TRPM2-KO mice than in WT mice, while plasma insulin levels were similar. β-cells isolated from TRPM2-KO mice produced smaller Ca^{2+} signals in response to high concentrations of glucose and incretin hormone than WT cells, resulting in reduced insulin secretion from pancreatic islets of these mice. Insulin secretion via TRPM2 seems to not only depend on the control of intracellular Ca^{2+} concentrations, but also occurs through Ca^{2+} influx-independent mechanisms (Uchida and Tominaga 2011; Uchida et al. 2011). Additionally, TRPM2 deletion is thought to protect mice from developing diet-induced obesity and insulin resistance (Zhang et al. 2012).

TRPM2 downregulation has also been shown to protect vascular endothelial cells from both H_2O_2- and tumor necrosis factor (TNF)α-induced apoptotic cell death (Sun et al. 2012). TRPM2 channels may further be important for disrupting the bronchial epithelial tight junctions, since their activation by oxidative stress induced the attenuation of the junctions through phospholipase Cγ1 (PLCγ1) and the protein kinase Cα (PKCα) signaling cascade (Xu et al. 2013b).

A somewhat unusual role and activation mechanism has been proposed for the ΔC splice variant of TRPM2 found in HeLa cells. Here it has been suggested that the truncated TRPM2 channel is activated following exposure to hypertonic solutions.

7 Lessons from Knockouts

Different strategies have been applied to study TRPM2 pathophysiological functions, including gene knockout. Several studies carried out in mice have shown that TRPM2 channels play a crucial role in the inflammatory process. Indeed, It was found that antigen-stimulated degranulation was significantly reduced in mucosal-type bone marrow-derived mast cells (mBMMCs) isolated from TRPM2-KO mice (Oda et al. 2013). Moreover, macrophages and microglia derived from this model organism show reduced production of chemokine (C-X-C motif) ligand-2 (CXCL2) and nitric oxide synthase induction (Haraguchi et al. 2012). Additionally, TRPM2 ablation revealed a prominent role of TRPM2 in the dextran sulfate sodium (DSS)-induced chronic experimental colitis mouse

model (Yamamoto et al. 2008), in which monocytes, neutrophils, and macrophages are the primary mediators of inflammation. This study demonstrated that in monocytes from TRPM2-deficient mice, the H_2O_2-induced Ca^{2+} influx and the production of the macrophage inflammatory protein-2 (CXCL2) were impaired. The impaired chemokine production in cells lacking TRPM2 was linked to a defect in TRPM2-mediated Ca^{2+} influx that consequently resulted in defective activation of the Ca^{2+}-dependent kinase Pyk2 and downstream activation of the Erk/NF-κB pathway (Yamamoto et al. 2008, 2010). In the DSS-induced colitis inflammation model, CXCL2 expression, neutrophil infiltration, and ulceration were all attenuated by TRPM2 disruption, suggesting that TRPM2-mediated Ca^{2+} influx controls the ROS-induced signaling cascade responsible for chemokine production and the aggravation of inflammation (Yamamoto et al. 2008).

Given that ROS play an important role in airway disorders such as adult respiratory distress syndrome (ARDS), cystic fibrosis, idiopathic fibrosis, chronic obstructive pulmonary diseases (COPD), and asthma, it is surprising that TRPM2 channels appear to not be critical for at least two airway inflammation models. Two recent publications that took advantage of TRPM2-KO mice have found no obvious or significant role for TRPM2 channels in chronic obstructive pulmonary disease in mice exposed to ozone, LPS, or tobacco smoke (Hardaker et al. 2012) or in a mouse airway inflammation model of OVA-induced severe allergic asthma (Sumoza-Toledo et al. 2011).

Since TRPM2 is also expressed in pancreatic β-cells, its role in insulin release has been confirmed through the use of transgenic animals. TRPM2-KO mice show impaired glucose tolerance and reduced insulin secretion, suggesting that TRPM2 contributes to the Ca^{2+} signals and insulin secretion in pancreatic β-cells and might represent a new factor involved in diabetes (Uchida and Tominaga 2011; Uchida et al. 2011).

8 Role in Hereditary and Acquired Diseases

Based on their reported physiological functions, much attention has been dedicated to investigating the role of dysfunctional expression and/or activity of TRPM2 channels in various pathological contexts. Since TRPM2 is most abundantly expressed in the brain, it is not surprising that TRPM2 has also been associated with CNS pathologies, including ischemia and neurodegenerative diseases (Xie et al. 2010). TRPM2 activation following in vitro ischemia increases cell death of male hippocampal neurons (Verma et al. 2012), and in stroke models, TRPM2 inhibition or knockdown is neuroprotective against ischemia in vitro and in vivo (Jia et al. 2011). TRPM2 appears to also be involved in mediating neuronal death of striatal neurons, which are particularly vulnerable to hypoxia-/ischemia-induced damage, and free radicals are thought to be prime mediators of this neuronal destruction (Smith et al. 2003). Recent work suggests that the observed preferential susceptibility of male neurons to TRPM2-mediated cell death may additionally involve androgen signaling and activation of the PARP pathway (Shimizu

et al. 2013). Furthermore, TRPM2 may contribute to neuropathic pain by aggravating pro-nociceptive inflammatory responses and sensitizing the pain-signaling pathway (Haraguchi et al. 2012).

Patients with bipolar disorders type I present high basal $[Ca^{2+}]_i$, and the chromosome region 21q22.3 harbors genes that confer susceptibility to this pathology, including TRPM2 (Xu et al. 2006, 2009, 2013a; Roedding et al. 2012, 2013). Although TRPM2 variants with a single amino substitution (e.g., Asp543Glu) have been detected in patients with bipolar disorder, the relevance of these variants in the pathogenesis of the disease remains to be elucidated. Additionally, TRPM2 has been shown to contribute to the expression of juvenile myoclonic epilepsy (JME) phenotypes by mediating disruptive effects of JME mutations of EFHC1 protein on biological processes such as cell death (Katano et al. 2012). TRPM2 has also been linked to amyotrophic lateral sclerosis and parkinsonism–dementia (Hermosura and Garruto 2007). Here, a TRPM2 mutation (P1018L) results in channels that inactivate more rapidly than wild-type channels, resulting in reduced Ca^{2+} entry. Again, the cellular and functional context of TRPM2 in these pathologies remains to be demonstrated.

The presence of TRPM2 in pancreatic β-cells and its role in glucose-induced insulin secretion suggest a possible role of this channel in diabetes (Herson and Ashford 1997, 1999; Togashi et al. 2006; Uchida et al. 2011). Insulin release was shown to be impaired in the TRMP2-KO mice treated by glucose and incretin hormone (Uchida et al. 2011). In contrast, Romero and collaborators reported the absence of any correlation between type 2 diabetes mellitus and the genetic TRPM2 variants rs2838553, rs2838554, rs4818917, rs1619968, rs1785452, rs2238725, rs2010779, rs9979491, and rs1573477 (Romero et al. 2010). However, the variants rs2838553, rs2838554, and rs4818917 showed negative association with a homeostatic model assessment of β-cell function, which determines insulin resistance and β-cell function, hinting at the possibility that TRPM2 activity may indeed regulate β-cell function. Further studies examining other variants are necessary to establish a role of TRPM2 in diabetes.

The above-described role of TRPM2 in the immune system function makes it a good candidate in promoting inflammatory diseases. TRPM2 expressed in macrophages and microglia aggravates peripheral and spinal pro-nociceptive inflammatory responses and contributes to the pathogenesis of inflammatory and neuropathic pain (Haraguchi et al. 2012). TRPM2 may also be the target of NLRP3 inflammasome-associated inflammatory disorders, since TRPM2 was shown to be the key factor that links oxidative stress to the NLRP3 inflammasome activation (Zhong et al. 2013). In cardiac tissue, accumulation of neutrophils in the reperfused area mediated by TRPM2 activation is likely to play a crucial role in myocardial I/R injury (Hiroi et al. 2013b). While TRPM2 is clearly linked to several inflammatory pathology models, it has been shown inconsequential in others. Hardaker and collaborators have reported that TRPM2 has no role in inflammatory mouse models of COPD (Hardaker et al. 2012), and Sumoza-Toledo et al. showed that TRPM2 is not required for airway inflammation in OVA-induced airway inflammation (Sumoza-Toledo et al. 2013).

Finally, TRPM2 may also play a role in cancer, where cytokine secretion by cancer cells contributes to cancer-induced symptoms and angiogenesis. The sirtuin SIRT6 was shown to promote cytokine secretion and migration in pancreatic cancer cells by increasing intracellular levels of ADP-ribose and consequently TRPM2-mediated Ca^{2+} mobilization. This calcium entry activates the Ca^{2+}-dependent transcription factors (NFAT) and thereby the expression of proinflammatory, proangiogenic, and chemotactic cytokines (TNF and IL-8) (Bauer et al. 2012). In human lung cancer A549 cells, activation of TRPM2 channel, which mediates ATP release, plays significant roles in the cellular responses to DNA damage induced by γ-irradiation and UVB irradiation (Masumoto et al. 2013). Similarly, therapeutic irradiation treatment as used in head and neck cancer treatments leads to activation of TRPM2 via stimulation of PARP1 and contributes to irreversible loss of salivary gland function (Liu et al. 2013). Finally, TRPM2 isoforms have been shown to play a crucial and differential role in neuroblastoma. Indeed, overexpression of TRPM2-S isoform in the neuroblastoma SH-SY5Y cell line results in increased proliferation through phosphatidylinositol 3-kinase/Akt and ERK pathways while overexpression of TRPM2-L isoform in confers protection against oxidative stress-induced cell death through FOXO3a and SOD (Chen et al. 2013). A more direct role in cell proliferation has been established in prostate cancer, where selective knockdown of TRPM2 inhibited the growth of prostate cancer cells but not of noncancerous cells. Moreover, subcellular localization of this protein was also remarkably different between cancerous and noncancerous cells, with benign cells expressing TRPM2 homogenously near the plasma membrane and in the cytoplasm, whereas in cancerous cells, a significant amount of the TRPM2 protein was clustered in the nucleus (Zeng et al. 2010).

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