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Review

Oxidative stress-modulated TRPM ion channels in cell dysfunction and pathological conditions in humans

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ABSTRACT

The transient receptor potential melastatin (TRPM) protein family is an extensive group of ion channels expressed in several types of mammalian cells. Many studies have shown that these channels are crucial for performing several physiological functions. Additionally, a large body of evidence indicates that these channels are also involved in numerous human diseases, known as channelopathies.
A characteristic event frequently observed during pathological states is the raising in intracellular oxidative agents over reducing molecules, shifting the redox balance and inducing oxidative stress. In particular, three members of the TRPM subfamily, TRPM2, TRPM4 and TRPM7, share the remarkable feature that their activities are modulated by oxidative stress.
Because of the increase in oxidative stress, these TRPM channels function aberrantly, promoting the onset and development of diseases.
Increases, absences, or modifications in the function of these redox-modulated TRPM channels are associated with cell dysfunction and human pathologies. Therefore, the effect of oxidative stress on ion channels becomes an essential part of the pathogenic mechanism. Thus, oxidative stress-modulated ion channels are more susceptible to generating pathological states than oxidant-independent channels.
This review examines the most relevant findings regarding the participation of the oxidative stress-modulated TRPM ion channels, TRPM2, TRPM4, and TRPM7, in human diseases. In addition, the potential roles of these channels as therapeutic tools and targets for drug design are discussed.

Contents

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1. Introduction

The transient receptor potential (TRP) protein ion channel family is expressed in several organisms, including worms, drosophila, and mammals [1–3]. The *trp* gene was first described by Montell & Rubin using Drosophila-based experiments [4]. The TRP family is divided into six main subfamilies based on their protein sequence homology: canonical (TRPC), vanilloid (TRPV), ankyrin (TRPA), polycystic kidney disease (TRPP), mucolipin (TRPML), and melastatin (TRPM) (Fig. 1). TRP channels have six predicted transmembrane domains and a pore region between the fifth and sixth transmembrane domains (Fig. 2) [5–8]. These ion channels are involved in several physiological processes, including vessel tone control, sensory perception, proliferation, and cell survival and death [1–3,9,10].

The TRPM subfamily takes its name from the first described member, melastatin (TRPM1), a protein identified as a potential tumor suppressor [11,12]. Currently, 8 proteins belong to this family. Most members of the TRPM subfamily are Ca^{2+}-permeable and Ca^{2+}-activated proteins, often associated with sensory perception systems [13,14]. However, a large body of evidence has shown that members of this family are involved in additional roles critical for maintaining cellular homeostasis and organ function. Thus, alterations in TRPM ion channel activity will affect physiological functions, prompting the onset of pathological states. Few ion channels have the unique feature of being modulated by oxidative stress at micromolar concentrations [15–22]. The activity of some members of the TRPM subfamily is modulated by oxidative stress [23]. Specifically, three members of the TRPM subfamily have emerged as the most important oxidative stress-modulated TRPM ion channels: TRPM2, TRPM4, and TRPM7 (Fig. 3). These channels are involved in several normal physiological processes as well as a number of human diseases. Reactive oxygen species (ROS) are able to modify the function of these TRPM channels, producing functional changes, which become imbalances in cellular homeostasis. Consequently, several processes regulated by these channels are modified by oxidative stress generating a pathological phenotype.

Moderate increases in intracellular ROS perform normal cellular functions [24]. However, a large increase in intracellular oxidative stress is a hallmark of several human diseases [24,25]. Thus, oxidative stress participates in cell proliferation [26,27], cell volume regulation [27], fibrosis [28,29], and several other functions.

Because an oxidative environment appears to be a factor in almost all pathologies, the occurrence of oxidative stress-modulated ion channels in an oxidative environment generates a favorable scenario for disease development. In contrast to oxidant-induced protein destruction, with its consequent loss of function, these oxidative-sensitive ion channels respond to oxidant molecules by modifying their function into aberrant behavior, generating pathological states.

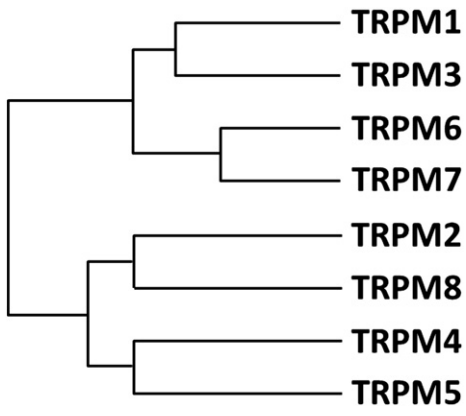

Fig. 1. Phylogenetic tree of the transient receptor potential (TRP) melastatin (TRPM) channel subfamily.

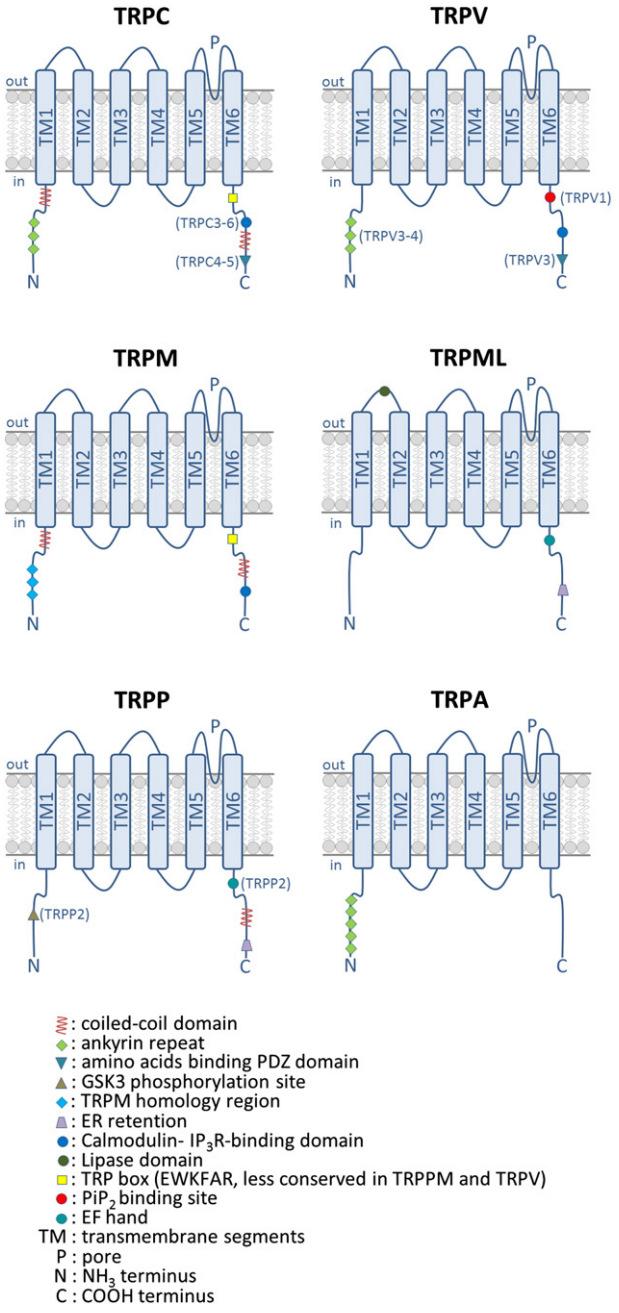

Fig. 2. Schematic structure of the six main subfamilies of TRP channels based on their protein sequence homology. NH_3 and COOH termini are cytoplasmic. Channels are drawn as a linear representation embedded in the lipid bilayer of the cell membrane. Domains not drawn to scale. The diagram highlights some structural features of TRP channels. TRPC: canonical; TRPV: vanilloid, TRPA: ankyrin; TRPP: polycystic kidney disease, TRPML: mucolipin, and TRPM melastatin.

In this review, we focused on describing and discussing the relevant studies regarding the involvement of the oxidative stress-modulated ion channels, TRPM2, TRPM4, and TRPM7, in cell dysfunction and human pathology.

2. Properties of the oxidative stress-modulated ion channels: TRPM2, TRPM4, and TRPM7

2.1. TRPM2

The TRPM2 ion channel (also known as LTRPC2 and TrpC7) is permeable to divalent ions such as Ca^{2+} and Mg^{2+}, and to monovalent

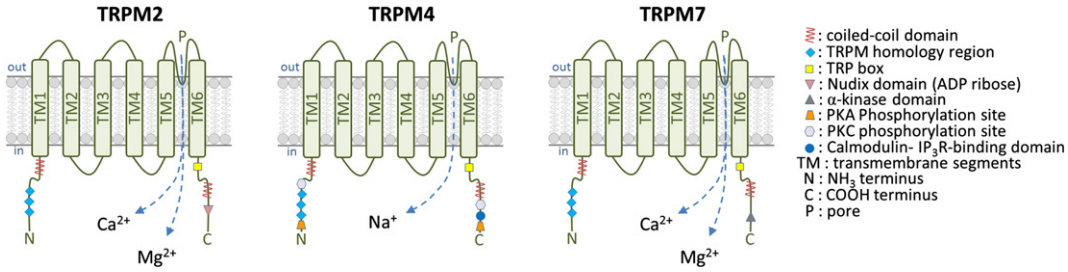

Fig. 3. Schematic structure, predicted topology and functional sites of the stress oxidative-modulated TRPM channels based on their protein sequence homology. NH_3 and COOH termini are cytoplasmic. Channels are drawn as a linear representation embedded in the lipid bilayer of the cell membrane. The diagram highlights some structural features of TRPM channels. Domains not drawn to scale.

ions, such as Na^+ and K^+ [30] (Fig. 2). TRPM2 was first cloned by Nagamine and coworkers [31]. Its structure contains an enzymatic region with ADP-ribose (ADPR)-hydrolase activity [32,33]. TRPM2 is expressed in several cell types, including microglial cells [34,35], neutrophil granulocytes [36,37], immune cells [32,33], insulin-secreting cells [38–40], neurons [41–43], and arterial endothelial cells [44].

In normal physiological states, the principal role of TRPM2 is to modulate the immune system by controlling cytokine release control in human monocytes, including tumor necrosis factor-alpha (TNFα), interleukin 6 (IL-6), IL-8, and IL-10 [45–47], and the maturation and chemotaxis of dendritic cells [48]. Additional functions of TRPM2 include the regulation of endothelial permeability [49] and insulin secretion [39,40].

A number of signals can activate the TRPM2 gating mechanism, both directly and indirectly. For instance, ADPR activates the channel by binding to the TRPM2 COOH-terminal NUDT9 domain [14,32,50]. ADPR-induced TRPM2 activation is strongly dependent on the intracellular Ca^{2+} concentration [51–53]. This Ca^{2+}-dependent activation of TRPM2 occurs through binding to the Ca^{2+}-sensing protein activity, calmodulin (CaM) [54]. NAD^+ and cyclic ADPR can also induce the opening of the TRPM2 channel [33,34,55–57]. TRPM2 is quickly and reversibly inhibited by 2-aminoethoxydiphenyl borate (2-APB) in contrast to the gradual or irreversible inhibition obtained using flufenamic acid, miconazole or clotrimazole [58]. Interestingly, TRPM2 is activated when TNFα links the activity of this channel to the immune system response [30,54].

The modulation of TRPM2 by oxidative stress is one of its most remarkable features. The first evidence indicating that TRPM2 activity is modulated by oxidative stress was reported in rat pancreas cells [59–62]. Later, unequivocal evidence demonstrated the connection between TRPM2 activity and oxidative stress [30,56,63]. Cells expressing endogenous or transfected TRPM2 that are exposed to micromolar H_2O_2 levels, show an increased TRPM2 current. This activation is dependent on an increase in intracellular NAD^+ levels followed by a direct interaction between NAD^+ and TRPM2 [30]. Similar results have been obtained using tert-butylhydroperoxide, tBOOH. However, no apparent oxidation of cysteine or methionine has been detected. Therefore, intracellular oxidants increase the amount of NAD^+ (oxidized from) over NADH (reduced form), promoting the activation of the channel [30]. This finding, indicates that the H_2O_2-activation of TRPM2 is indirect.

Single-channel currents recorded after the heterologous expression of TRPM2 in CHO cells exhibit an ADPR-induced TRPM2 conductance of ~50 pS, while the H_2O_2-induced conductance is ~40 pS [64]. These results suggest that ADPR and H_2O_2 have independent activation mechanisms. Furthermore, the TRPM2 current activated by H_2O_2 remains dependent on Ca^{2+}/CaM activity. Site-directed mutagenesis to produce an aspartic acid replacement in the CaM Ca^{2+}-binding EF hand motifs abolishes the TRPM2-mediated Ca^{2+} influx elicited in response to H_2O_2 challenge [54]. However, despite the strong body of data linking ROS action to TRPM2 activity, the exact molecular mechanism by which oxidative stress modulates TRPM2 activity is far from being completely elucidated. The effect of antioxidants and reducing agents on H_2O_2-induced TRPM2 currents has been studied. The intracellular depletion of glutathione in its reduced form (GSH) using an inhibitor of GSH synthesis is capable of activating both the TRPM2 current density and the TRPM2-mediated Ca^{2+} influx in dorsal root ganglion (DRG) neurons, which are inhibited by the addition of 2-APB or GSH [65]. In addition, pharmacological evidence suggests that TRPM2 is involved in the oxidative injury in the brain and DRG caused by 2.45 GHz electromagnetic radiation (EMR) [66]. Furthermore, the use of antioxidant agents increased cell viability, consistent with the ROS modulation of TRPM2 [66]. In contrast, extracellular or intracellular administration of GSH, as well as vitamins C and E, do not inhibit the H_2O_2-induced TRPM2 current in CHO cells [67], suggesting that the ROS modification of TRPM2 current may be cell-type specific.

In addition, structural properties also affect the oxidative modulation of TRPM2. The N-terminus deletion of amino acids, from 538 to 557 (TRPM2-ΔN), acts as a dominant negative mutant of TRPM2. HEK 293 cells transfected with TRPM2-ΔN exhibit protection against an H_2O_2 challenge [56]. Similarly, in addition to the typical TRPM2 isoform, a shorter isoform has been cloned (TRPM2-S) that lacks the third to sixth transmembrane domains. This short form of TRPM2 interacts directly with the full-length (TRPM-L), acting as a dominant negative mutant by inhibiting the TRPM2-mediated Ca^{2+} influx. Interestingly, in contrast to the extensive cell death induced by H_2O_2 exposure in cells transfected with TRPM2-L, the simultaneous transfection of TRPM2-L and TRPM2-S suppresses the H_2O_2-induced cell death by inhibiting of the oxidative stress-induced TRPM2 activity [68]. This finding suggests that the dominant negative actions of TRPM2-S protect cells from the oxidative insult.

2.2. TRPM4

The TRPM4 ion channel is a Ca^{2+}-activated non-selective cation channel permeable to monovalent cation such as Na^+ and K^+ [69,70] (Fig. 2). TRPM4 is expressed in a number of tissues, such as arterial endothelial cells [44], vein endothelial cells [71], immune cells [72], neurons [41], smooth muscle cells [73], pancreatic islet β-cells [74], and others. TRPM4 performs a number of physiological functions including modulating the plasma membrane potential [69,70], regulating Ca^{2+} overloading [69], producing and secreting IL-2 from T lymphocytes [72], and regulating cerebral artery constriction [73,75–77].

TRPM4 was first cloned and characterized by Launay and coworkers [69]. Two splice variants, or isoforms, of TRPM4 have been described: a short form, TRPM4a, in which 174 amino acids residues were deleted from the N-terminus [78], and a long version, TRPM4b (referred to as TRPM4 throughout this review) [69]. The large version of TRPM4 is virtually impermeable to divalent ions, including Ca^{2+} and Mg^{2+} [69]. In contrast, TRPM4a is a Ca^{2+}-permeable channel [78]. The tetramerization of TRPM4b subunits is required to form

the proper channel structure. However, heterotetramers of TRPM4a and TRPM4b subunits are also possible. In fact, an experiment performed using fluorescence resonance energy transfer (FRET) showed that TRPM4a and TRPM4b gathered around each other, suggesting a potential coupling of these two isoforms [79].

Nilius and coworkers delved deeper in the electrophysiological properties of TRPM4 [70]. TRPM4 is activated when the intracellular Ca^{2+} concentration increases. This activation is followed by a fast desensitization, observed principally in the whole-cell configuration. Furthermore, TRPM4 exhibits a voltage-dependent modulation, that is not capable of activating the channel, showing a strong outward rectification [70,79,80]. This voltage dependence is modulated by decavanadate, which inhibits the voltage-dependence closure of the channel [81] In addition, TRPM4 is blocked by intracellular nucleotides and polyamines such as ATP, ADP, AMP, adenosine, spermidine, and spermine [82]. Moreover, it has been reported the inhibition of TRPM4 activity by using the sulphonylurea, glibenclamide [83]. This agent is a well-known ATP-binding cassette proteins (ABC protein) blocker [84,85]. The inhibitory effect of glibenclamide is supported on the basis that TRPM4 ion channel contains two ABC transporter signature-like motifs [81]. The hydroxytricyclic derivative, 9-phenanthrol, specifically inhibits TRPM4 without effect on its homologue TRPM5 [86].

In addition to increments in the intracellular Ca^{2+} concentration, the membrane phospholipid, phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$), also modulates the channel activity by controlling channel desensitization [14,87,88].

Oxidative stress also modulates TRPM4 activity. In cells expressing TRPM4, exposure to H_2O_2 abolishes the channel deactivation, leading to sustained TRPM4 activity without changes in the $[Ca^{2+}]_i$ dependence [18]. Site-directed mutagenesis of cysteine 1093 (Cys^{1093}) into alanine, prevents H_2O_2-mediated TRPM4 desensitization, indicating that Cys^{1093} is crucial in removing the channel desensitization [18]. Interestingly, this cysteine is located next to several arginine and proline residues, reducing the p*Ka* of Cys^{1093}, and enhancing its reactivity to ROS. Accordingly, overexpression of TRPM4 renders cells vulnerable to H_2O_2-induced cell death. In addition, TRPM4 knockdown has been shown to be effective in abolishing the susceptibility for H_2O_2-induced cell death, in which ROS-sensitive Cys^{1093} was shown to be responsible for conferring the vulnerability to H_2O_2 [18]. Furthermore, the LPS-derived generation of ROS modulates endogenous TRPM4 currents, suggesting that this effect is not limited to exogenous ROS, but is also affected by endogenous ROS production [71]. Additionally, ROS derived from trauma are also effective in modulating TRPM4 activity through incrementing TRPM4 expression in the injured region [89].

2.3. TRPM7

TRPM7 (previously named LTRPC7, TRP-PLIK, and ChaK1), originally cloned by Nadler and coworkers [90] is a Ca^{2+}-permeable ion channel that also has an atypical C-terminal Ser/Thr α-kinase kinase activity through its kinase domain, which has homology to that of elongation factor 2 (eEF2) [2,90,91]. Early characterization of TRPM7 showed currents which are activated by low Mg · ATP levels (called as magnesium-nucleotide-regulated metal ion current (MagNuM)) [41,90,92,93]. These channels have a homologue, TRPM6, which exhibits the same C-terminal intrinsic kinase activity. TRPM7 is also permeable to Mg^{2+}, and its current is inhibited by extracellular Zn^{2+} and Gd^{3+} [41,90,92]. TRPM7 has been shown to be slightly more permeable to Mg^{2+} than Ca^{2+} [90,94,95]. In the absence of extracellular divalent cations, TRPM7 conducts monovalent cations such as Na^+ [90,94,95]. Similarly to TRPM4, TRPM7 is also modulated by ($PI(4,5)P_2$) [96]. TRPM7 is widely expressed. For instance, TRPM7 is found in endothelial cells [44], monocytes [97], neurons [41,98,99], osteoblasts [100,101], mesenchymal stem cells [102], and vascular smooth muscle cells [103], among many other types of cells. TRPM7 activity contributes to several physiological functions, such as neurotransmitter release in sympathetic neurons [104], small synaptic-like vesicle fusion [105], the proliferation of and nitric oxide production by endothelial cells [106], and the regulation of the intracellular Mg^{2+} concentration [90,94,103].

The regulation of TRPM7 activity by oxidative stress has been known for a decade. Exposure to ROS activates TRPM7 currents [90,98]. In addition, TRPM7 currents are markedly enhanced by H_2O_2 exposure [98]. Furthermore, the mRNA and protein expression of TRPM7 are increased in cells exposed to oxidant agents [41,97]. Interestingly, TRPM7 overexpression enhances intracellular ROS levels [107]. TRPM7 overexpression-induced ROS generation may result from mitochondrial metabolism [107]. In fact, decreasing TRPM7 levels produces a concomitant decrement in intracellular ROS levels, dependent on Mg^{2+} levels, as well as resistance to the cell death induced by apoptotic stimuli [108]. All these findings indicate a potential positive feedback for TRPM7 activity in an oxidant environment.

Table 1 and Fig. 4, summarize all main properties of the oxidative stress-modulated TRPM ion channels described above.

3. Cellular function impairment, cell death, and human pathological conditions

Although TRPM channels are involved in several human pathologies, we focused here in those which the participation of the stress oxidative-modulated ion channels, TRPM2, TRPM4, and TRPM7, has been demonstrated (Fig. 5). Table 2 summarizes all main findings of the oxidative stress-modulated TRPM ion channels involved in pathological conditions in humans.

4. Inflammation and immune system activation

Globally, the role of ROS-modulated TRPM2 activity is linked to several inflammatory situations. For instance, in dextran sulfate sodium (DSS)-induced experimental colitis used as an ROS-related inflammation model, TRPM2-knockout (KO) mice show a reduction in several indicators of inflammation, including monocyte activation, neutrophil migration and infiltration, and ulceration [6,109]. Accordingly, TRPM2-KO mice are extremely vulnerable to infection with *Listeria monocytogenes*. The innate immune response of the TRPM2-KO mice is ineffective [47]. This vulnerability to bacterial infection may be understood by recalling that TRPM2 is required for cytokine production by monocytes [45]. Because TRPM2 is a thermosensitive channel, studies of the influence of oxidative stress in temperature sensing showed that H_2O_2 exposure was able to shift the temperature threshold for TRPM2 activation to lower temperatures, near physiological body values [110]. Single mutation experiments showed that this sensitization was promoted by the oxidation of methionine 214 [110]. This finding suggests that immune cell-derived oxidative stress modulates TRPM2 activity during inflammation and fever.

In addition, TRPM2-mediated Ca^{2+} influx is critical in the maturation and chemotaxis of dendritic cells (DCs), suggesting an essential effect in the immune system [48]. DCs lacking TRPM2 expression show a deficiency in chemokine-activated directional migration. Additionally, in a TRPM2-deficient DC model, the bacteria-induced DC trafficking in draining lymph nodes was impaired [48].

Furthermore, TRPM2 acts as a decisive factor modulating the phagocyte ROS generation that attenuates the effects of inflammation [46]. TRPM2 contributes to the depolarization of the phagocyte cell membrane, decreasing NAD(P)H oxidase-dependent ROS production. TRPM2-KO mice challenged with the endotoxin, lipopolysaccharide, show an exacerbated endotoxin-dependent lung inflammatory response as well as an elevated death score [46], suggesting that TRPM2 exerts a protective role against lung inflammation. However, several experiments performed in different models of chronic obstructive pulmonary disease (COPD) did not show different outcomes

Table 1
Properties of oxidative stress-modulated TRPM ion channels.

Channel	Ca^{2+} permeable	Activated by	Regulated by	Inhibited by	Expressed in	Proposed physiological function
TRPM2	Yes [30]	Ca^{2+} [54] H_2O_2 [30,56,63] cADPR [33,34,55–57]	ADPR [51–53]	2APB [58] Flufenamic acid [58] Miconazole [58] Clotrimazole [58]	Microglia [34,35] Neutrophil [36,37] Immune cells [32,33] Insulin secreting cells [38–40] Neurons [41–43] Arterial endothelial cells [44]	Immune system modulation [45–47] Dendritic cells maturation and chemotaxis [48] Endothelial permeability [49] Insulin secretion [39,40]
TRPM4	No [69,70]	Ca^{2+} [70,79,80]	H_2O_2 [18,71,89] PiP_2 [87,88]	Nucleotide[82] Polyamines [82] Miconazole [58] 9-phenantrole [86,135] Glibenclamide [83,135]	Vein endothelial cells [71] Immune cells [72] Pancreatic islets β-cells [74] Smooth muscle cells [38–40] Neurons [41] Arterial endothelial cells [44]	V_m modulation [69,70] Ca^{2+} overload [69] IL-2 secretion [72] Cerebral arterial constriction regulation [73,75–77]
TRPM7	Yes [90,94,95]	Mg^{2+}-ATP [41,90,92,93]	H_2O_2 [90,98] PiP_2 [96]	Zn^{2+}, Gd^{3+} [41,90,92]	Endothelial cells [44] Monocytes [97] Osteoblast [100,92] Vascular smooth muscle cells [103] Neurons [41,98,99] Mesenchymal stem cells [103]	Neurotransmitter release [104] Vesicle fusion [105] NO production [106] Endothelial cell proliferation [106] Mg^{2+} concentration regulation [90,94,103]

between TRPM2 KO mice and wild type animals in airway inflammation and immune cell activation [111]. These findings suggest that the roles played by TRPM2 in inflammation may be tissue specific. The above findings suggest that TRPM2, far from being an antagonist, has complementary actions in various immune cells.

With the body of evidence already presented, it is important to consider that the oxidative stress modulation of TRPM2 activity may be detrimental or beneficial, depending on the tissue or the pathology. This specificity requires the development of tissue-specific drugs to selectively inhibit or activate TRPM2 activity.

In the same context, TRPM4 could be also involved in an immune response during inflammation. Since TRPM4 is differentially expressed in Th1 and Th2 cells, this channel plays differential functions in each T cell subsets. Despite TRPM4 is not permeable to Ca^{2+}, the main proposed role of TRPM4 is to control Ca^{2+} signaling, through its control of the membrane potential. Therefore, the downregulation of TRPM4 levels plays a distinctive role in T cell function by regulating Ca^{2+} signaling and the nuclear localization of NFATc1 [112]. In addition, TRPM4 controls the migration of bone marrow-derived mast cells (BMMCs), suggesting that TRPM4 perform an essential function in the migration of BMMCs by regulating Ca^{2+}-dependent actin cytoskeleton rearrangement [113]. Furthermore, TRPM4 also participates in DC function. TRPM4 activity is critical for DC migration because the suppression of the channel significantly decreased chemokine-dependent DC migration [114]. However, in contrast to TRPM2, TRPM4 does not affect in DC maturation [114].

Furthermore, TRPM4 has been involved in the control of monocytes and macrophages during sepsis syndrome [115]. Mortality of TRPM4-KO mice ($TRPM4^{-/-}$) undergo sepsis induced by cecal ligation and puncture as model of bacterial systemic infection, was severely increased suggesting a crucial role of TRPM4 for survival during sepsis [115]. This increase in the mortality score is supported by the finding that monocytes and macrophages activation is dependent on TRPM4 activity [115].

TRPM7 also participates in the immune system. The growth of TRPM7-KO B lymphocytes is arrested, leading to death. Mg^{2+} supplementation restores the proliferative status of B cells as well as their viability [116]. In addition, TRPM7 activity is a key factor in human mast cell survival. The downregulation of TRPM7 expression induces mast cell death, which is not prevented by increasing the concentration of extracellular Mg^{2+} [117]. Since TRPM7 is a Mg^{2+}-permeable ion channel, these results support the hypothesis that TRPM7 is a crucial protein for B cell activation and mast cell survival.

A global view of the inflammatory response and immune system activation induced by the oxidative stress-modulated TRPM ion channels is showed in Fig. 6A.

5. Neurodegenerative diseases and neurological disorders

TRPM2 has been linked to several neurodegenerative diseases. Cultured neurons transfected with small interfering RNA against rat TRPM2 are resistant to H_2O_2-induced neuronal death [118]. Similarly, A172 glioblastoma cells stably-transfected with TRPM2 are more vulnerable to H_2O_2-induced cell death compared to non-transfected cells [119]. Additionally, TRPM2 expressed in immune cells, such as microglia and macrophages, is able to intensify peripheral and spinal pro-nociceptive inflammatory responses. Furthermore, TRPM2 contributes to the development of inflammatory and neuropathic pain [120]. TRPM2 may also

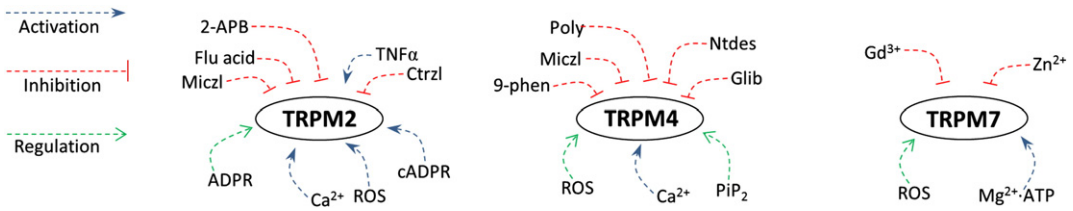

Fig. 4. The diagram shows the main agents promoting activation, inhibition and regulation of the stress oxidative-modulated TRPM channels. Activation, inhibition and regulation could be promoted by a direct and/or indirect way. Channels are drawn embedded in the lipid bilayer of the cell membrane. Domains not drawn to scale. 2-APB: 2-aminoethoxy diphenyl borate; Flu acid: Flufenamic acid; Ctrzl: Clotrimazole; TNF-α: Tumor necrosis factor α; ADPR: ADP-Ribose; Glib: Glibenclamide; 9-phen: 9-phenantrol; Poly: Polyamines; Ntdes: Nucleotides; Miczl: Miconazole; ROS: Reactive oxygen species; PiP_2: phosphatidylinositol 4, 5-bisphosphate.

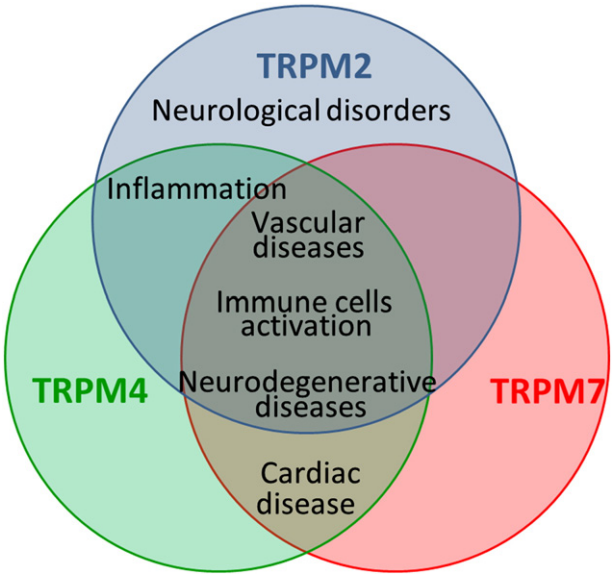

Fig. 5. Diagram of the human pathologies induced by the oxidative stress-modulated TRPM ion channels, TRPM2 (blue), TRPM4 (green) and TRPM7 (red).

be overexpressed in activated glial cells during ischemic injuries produced via a middle cerebral artery occlusion stroke model in rats. Because post-ischemic damage is mostly mediated by an increase in oxidative stress, TRPM2 may play a major role in ischemia-induced neuronal death [35]. Furthermore, the cerebral cortex and hippocampus of animals subjected to a traumatic brain injury (TBI) show an increment in TRPM2 mRNA expression [121], suggesting that this channel may contribute to TBI-induced deleterious effects. Interestingly, TRPM2 contributes to the features of emerging juvenile myoclonic epilepsy (JME). TRPM2 and the EF-hand motif-containing protein (EFHC1) are co-expressed and physically connected in hippocampal neurons and ventricle cells. EFHC1 potentiates both the H_2O_2- and ADPR-induced TRPM2 current as well as the TRPM2-induced Ca^{2+} influx. Furthermore, EFHC1 enhances the susceptibility to H_2O_2-induced TRPM2-mediated cell death. Thus, TRPM2 generates the apoptotic neuronal death induced by the EFHC1 mutation in JME [122]. Additionally, TRPM2 may be involved in Alzheimer's disease (AD). Neuronal death induced by beta amyloid protein (Aβ) accumulation in the brain is a crucial factor underlying AD [123,124]. TRPM2 activity is involved in Aβ-induced striatal neuron death through abnormal increases in the intracellular Ca^{2+} concentration [123,124]. Moreover, dopaminergic neurons of the rat substantia nigra express TRPM2 which may be responsible for H_2O_2-induced Ca^{2+} influx. Because neurons in Parkinson's disease exhibit an oxidative stress increment, TRPM2 may also be involved in Parkinson's disease [42]. TRPM2 is a candidate for conferring susceptibility to Western Pacific Guamanian amyotrophic lateral sclerosis (ALS-G) and Guamanian Parkinson-derived dementia (PD-G), suggesting that the function of TRPM2 is associated with motor neuron death [125,126]. A missense mutation of TRPM2 that changed proline 1018 to leucine contributed to the occurrence of the pathological disease [125,126]. Additionally, TRPM2 has been associated with bipolar disorder. In a case–control study, TRPM2 single-nucleotide polymorphisms were significantly associated with conferring risk for bipolar disorder [127–129].

TRPM4 has been linked to the progression of secondary hemorrhages induced by spinal cord injury (SCI) [89]. A secondary hemorrhage results from the loss of the integrity of capillaries and small vessels that occurs after a traumatic injury. Secondary hemorrhages enhance the volume of the site of primary injury and are deleterious to the function of the central nervous system (CNS). The suppression of TRPM4 expression, via either the intravenous administration of TRPM4 antisense in rats or TRPM4-KO mice ($TRPM4^{-/-}$), is completely effective in improving the outcome after SCI [89]. TRPM4 inhibition is effective in reducing the fragmentation of capillaries, reducing hemorrhage development, and inhibiting neurological detriment [89].

Furthermore, TRPM4 has been involved in multiple sclerosis, a neurodegenerative disease caused by a chronic inflammation in of the CNS [130]. TRPM4-KO mice ($TRPM4^{-/-}$) undergo experimental autoimmune encephalomyelitis (EAE) showed reduced axonal and neuronal degeneration and reduced clinical disease scores compared to wild-type animals without affecting EAE-induced autoimmune responses [130]. These results demonstrate that TRPM4 is crucial in the pathogenesis of inflammation-induced axonal and neuronal injury.

ROS-enhanced TRPM7 activity is crucial for the death of cortical neurons during prolonged oxygen-glucose deprivation (OGD) [98]. Of note, TRPM7 overexpression itself results in cell death [90,98]. Thus, the downregulation of TRPM7 expression protects cortical neurons from OGD-induced anoxia [98]. Neuronal death induced by pathophysiologically relevant H_2O_2 concentrations is induced by a mechanism dependent on increases in the intracellular Ca^{2+} concentration [99]. Similarly, ROS-induced neuronal death by exposure to LPS is mediated by TRPM7 [41]. LPS exposure induces dose-dependent neuronal death in a mechanism dependent on NAD(P)H oxidase-derived ROS generation. The suppression of TRPM7 expression efficiently abolishes LPS-induced neuronal death in both primary hippocampal neurons and pheochromocytoma-derived sympathetic neurons [41]. Considering all these results, the TRPM7 protein emerges as a key factor in ROS-dependent neuronal death. Extending the results found in neuron culture experiments, TRPM7 has been found to perform several pathological functions related to the CNS in whole animals. The brain ischemia induced by a cardiac arrest model caused a delayed hippocampal CA1 in neurons, generating cognitive impairment [131]. Because TRPM7-KO mice are non-viable, stereotactic microinjections of viral shRNA against TRPM7 into the hippocampus were performed to suppress TRPM7 activity, showing that infected hippocampal neurons were resistant to ischemia. Additionally, TRPM7 suppression preserved cognitive skills [131]. Similarly to TRPM2, TRPM7 is also a candidate for conferring susceptibility to Western Pacific ALS-G and PD-G. A heterozygous variant of TRPM7 with a missense mutation in which threonine 1482 is replaced with isoleucine would confer a genetic predisposition to ALS/PD [125].

Fig. 6B shows a diagram of the neurodegenerative diseases and neurological disorders induced by the oxidative stress-modulated TRPM ion channels.

6. Heart and vascular diseases

Aside from the actions in the nervous system, these channels also participation in pathologies affecting the cardiovascular system. The oxidative stress modulation of TRPM2 has implications in endothelial barrier dysfunction. H_2O_2 exposure promotes an increase in endothelial permeability via a TRPM2-dependent Ca^{2+} influx [132]. Alterations in the transendothelial resistance (TER) induced by H_2O_2 decrease by ~50% when the TRPM2 activity is suppressed [132], suggesting that at least half of the H_2O_2-induced TER is mediated by TRPM2.

TRPM4 is also linked to cardiovascular diseases. This channel has been associated with progressive familial heart block type I (PFHBI). TRPM4 activity is associated with the control of cardiac electrical conduction in Purkinje fibers, cardiomyocytes, and sinoatrial node cells. A missense mutation in TRPM4, in which glycine 19 was replaced by alanine, was found in patients who carried an autosomal-dominant form of PFHBI [133]. This mutation enhances the Small Ubiquitin MOdifier conjugation (SUMOylation) of the channel by attenuating the deSUMOylation processes. Because of the constitutive SUMOylation, TRPM4 endocytosis is impaired in this mutant, maintaining an augmented TRPM4 density at the plasma membrane, which incremented TRPM4 activity and suggested an abnormal control of cardiac conduction [133,134]. In addition, experiments using the selective TRPM4

Table 2
Oxidative stress-modulated TRPM ion channels in pathological conditions.

Channel	Pathological condition	Main findings	Experimental platform	Refs.
TRPM2	DSS-induced experimental colitis	–Reduced monocyte activation in the KO mice –Reduced neutrophil migration and infiltration in the KO mice –Reduced ulceration in the KO mice	TRPM2-KO mice	[6,109]
	Monocytes activation by endotoxin	–TRPM2-dependent cytoquine production	Human primary monocytes and TRPM2 downregulation by shRNA	[45]
	Infection with *Listeria monocytogenes*	–Ineffective innate immune response in the KO mice	TRPM2-KO mice	[47]
	Bacterial infection	–Impaired bacteria-induced DC trafficking in draining lymph nodes –Impaired maduration of DCs –Reduced chemotaxis of DCs	TRPM2-deficient DC model	[48]
	Endotoxin administration	–Exacerbated endotoxin-dependent lung inflammatory response –Elevated mortality	TRPM2-KO mice	[46]
	Chronic obstructive pulmonary disease	–No different outcomes between KO mice and WT animals in airway	TRPM2-KO mice	[111]
	Neurons exposed to H_2O_2	–Reduced oxidative stress-induced neuronal death	TRPM2 downregulation by siRNA	[118]
	Glioblastoma cells exposed to H_2O_2	–Increased oxidative stress-induced death	TRPM2 upregulation by transfection	[119]
	Ischemic injury	–TRPM2 overexpression in glial cells	Stroke model in rats	[35]
	Traumatic brain injury	–TRPM2 overexpression in cerebral cortex and hippocampus	Trauma model in rats	[121]
	Juvenile myoclonic epilepsy	–TRPM2-dependent apoptotic neuronal death induced by the EFHC1 mutation in JME	TRPM2 expression in HEK293 cells	[122]
	Alzheimer's disease	–TRPM2 activity is involved in beta amyloid protein-induced striatal neuron death through increases in the $[Ca^{2+}]_i$	Rat primary striatum cultures and TRPM2 downregulation by siRNA	[123,125]
	Guamanian Amyotrophic lateral sclerosis (ALS-G)	— Mutation of TRPM2 contributes to the occurrence of ALS-G	Human brain samples	[125,126]
	Guamanian Parkinson-derived dementia (PD-G)	–Mutation of TRPM2 contributes to the occurrence of PD-G	Human brain samples	[125,126]
	Bipolar disorder	–TRPM2 single-nucleotide polymorphisms are associated with conferring risk for bipolar disorder	Case–control study	[127,129]
	Endothelial cells exposed to H_2O_2	–Reduction in H_2O_2-induced transendothelial premeability	TRPM2 downregulation by siRNA	[132]
	Melanoma	–TRPM2 mRNA levels are upregulated	qPCR, antisense oligonucleotide	[139]
	Prostate cancer	–TRPM2 downregulation inhibit cancer cells proliferation	TRPM2 downregulation by siRNA	[140]
	Control of glycemia	–Malfunction of renal clearance of glucose	TRPM2-KO mice	[40]
	Insulinoma	–TRPM2 downregulation protects H_2O_2-induced β-cells death	Antisense oligonucleotide against TRPM2	[30,61]
TRPM4	Infection, inflammation	–Control of intracellular Ca^{2+} signaling –Nuclear localization of NFATc1	TRPM4 downregulation by siRNA and DN	[112]
	Infection, inflammation	–Control of migration of bone marrow-derived mast cells (BMMCs)	BMMCs from TRPM4 KO mice	[113]
	Infection, inflammation	–Decreased chemokine-dependent DC migration –No effects in DC maduration	DC from TRPM4 KO mice	[114]
	CLP-induced sepsis syndrome	–Reduced monocytes and macrophages activation –Elevated mortality	TRPM4-KO mice	[115]
	Spinal cord injury (SCI)	–Reduced fragmentation of capillaries in the KO mice –Reduced hemorrhage development in the KO mice –Reduced neurological detriment in the KO mice	TRPM4-KO mice	[89]
	Multiple sclerosis	–Reduced axonal and neuronal degeneration in the KO mice –Reduction of clinical disease scores in the KO mice	TRPM4-KO mice	[130]
	Progressive familial heart block type I (PFHBI)	–TRPM4 mutation is founded in patients with PFHBI –TRPM4 mutation augments channel activity by altered endocytosis	Family-genetic studies	[133,134]
	Early after-depolarization (EADs) arrhythmias	–EADs arrhythmias are abolished by 9-phenanthrol	TRPM4 inhibition by 9-phenanthrol	[135]
	Hypertension	–Hypertensive levels of blood pressure in the KO mice –Oversecretion of catecholamines from chromaffin cells, promoting increased levels of plasma epinephrine	TRPM4-KO mice	[136]
	Endotoxin exposure	–Reduced endotoxin-induced endothelial cell death	TRPM4 downregulation by siRNA	[71]
	$CD45^+$ lymphoma	–TRPM4 upregulation in $CD45^+$ lymphoma	Microarray in patient samples	[142]
	Cell line derived from tumors	–Cancer progression dependent on β-catenin	TRRPM4 downregulation by shRNA	[143]
	Glycemia control	–TRPM4 downregulation inhibits glucose-induced insulin secretion	TRPM4 downregulation using a dominant negative	[74,148]
TRPM7	B lymphocytes activation	–Reduced B lymphocytes growth	TRPM7-deficient B cells	[116]
	Human mast cell survival	–Increased death of mast cells	TRPM7 downregulation by siRNA	[117]
	Oxygen-glucose deprivation (OGD) *in vitro* model	–Reduced OGD-induced cortical neuron death	TRPM7 downregulation by antisense	[95]
	Neurons exposed to H_2O_2	–Reduced H_2O_2-induced neuronal death	TRPM7 downregulation by siRNA	[99]
	Neurons exposed to endotoxin	–Reduced endotoxin-induced neuronal death	TRPM7 downregulation by siRNA	[41]
	Brain ischemia model	–Reduced ischemia-induced neuronal death –Reduced cognitive impairment	Hippocampal TRPM7 shRNA	[131]
	Neurons exposed to endotoxin	–Reduced LPS-induced neuronal death	TRPM7 downregulation by siRNA	[41]
	Guamanian Amyotrophic lateral sclerosis (ALS-G)	–Mutation of TRPM7 confer predisposition to ALS-G	Human brain samples	[125]
	Guamanian Parkinson-derived dementia (PD-G)	–Mutation of TRPM7 confer predisposition to PD-G	Human brain samples	[125]

Table 2 (*continued*)

Channel	Pathological condition	Main findings	Experimental platform	Refs.
TRPM7	Spontaneously hypertensive rats (SHR)	–Decreased TRPM7 expression in SHR rats	Spontaneously hypertensive rats (SHR)	[137]
	Human gastric adenocarcinoma cells	–TRPM7 inhibition inhibits gastric adenocarcinoma cells proliferation	TRPM7 downregulation by siRNA	[145,153]
	Inherited hypomagnesemia	–TRPM7 downregulation is founded in Inherited hypomagnesemia	Mice bred for high or low intracellular Mg^{2+}	[150]
	Cadmium-induced osteoporosis	–TRPM7 downregulation decreases the Cd-induced osteoporosis	TRPM7 downregulation by siRNA	[101]

DSS: dextran sulfate sodium; DC: dentritic cell; CLP: cecal ligature and punction; JME: Juvenile myoclonic epilepsy; EFHC1: EF-hand motif-containing protein; SHR: spontaneously hypertensive rats; ALS-G: Guamanian amyotrophic lateral sclerosis; PD-G: Guamanian Parkinson-derived dementia; PFHBI: Progressive familial heart block type I; EADs: Early after-depolarization; SCI: Spinal cord injury.

inhibitor 9-phenanthrol linked this channel to cardiac arrhythmias [86]. Early after-depolarization (EADs) arrhythmias are abolished using 9-phenanthrol, suggesting that TRPM4 is involved in EADs [135]. Hypertension is also associated with TRPM4 activity. TRPM4-KO mice show hypertensive levels of blood pressure [136]. In addition, TRPM4 suppression causes the oversecretion of catecholamines from chromaffin cells, promoting increased levels of plasma epinephrine [136]. Thus, catecholamine oversecretion may contribute to hypertension. In addition, the ROS-dependent endothelial death induced by lipopolysaccharide exposure was dependent on TRPM4 activity [71]. The downregulation of TRPM4 expression protected a significant portion of endothelial cells from the ROS generated by the LPS challenge. This finding suggested that the intracellular oxidative environment was able to modify TRPM4 activity, consequently modifying cell homeostasis to promote endothelial cell death [71].

TRPM7 is also involved in hypertension by altering Mg^{2+} transport in vascular smooth muscle cells. The expression of TRPM7 in spontaneously hypertensive rats (SHR) is blunted. This downregulation correlates with the concomitant decrease in the intracellular Mg^{2+} concentration [137]. In addition, the upregulation of angiotensin II-induced TRPM7 expression produced in healthy animals was not detected in SHR [137]. Furthermore, TRPM7 has been connected to human atrial fibrillation mediated by fibrogenesis [138].

Fig. 6C shows the cardiac diseases and vascular dysfunction induced by the oxidative stress-modulated TRPM ion channels.

7. Cancer

TRPM2 mRNA levels are upregulated in melanomas in which the increased activity is coupled with the methylation of the CpG island [139]. Furthermore, TRPM2 silencing abolishes the proliferation of prostate cancer cells without affecting healthy cells [140]. This finding indicates that regulating the increment in TRPM2 activity in melanoma cells is a plausible therapeutic strategy against cancer progression.

A connection between cancer and TRPM4 has been reported [141]. TRPM4 mRNA expression is increased in CD5+ lymphomas, suggested that TRPM4 ion channel expression can be used as diagnostic marker [142]. In addition, the downregulation of TRPM4 expression promotes enhanced β-catenin degradation, whereas restoring TRPM4 expression increases cell proliferation [143], suggesting that TRPM4 participates in cancer progression in association with β-catenin. Consequently, TRPM4 inhibition may be a feasible therapeutic approach to cancer.

The experiments performed in the cutaneous melanophores of zebrafish showed that TRPM7 can prevent the accumulation of cytotoxic molecules derived from melanin synthesis, protecting melanocytes from death [144]. Additionally, the blockade of TRPM7 channel activity inhibited the growth and survival of human gastric adenocarcinoma cells [145,153], suggesting that TRPM7 also influences the proliferation of cancer cells and tumor growth. Thus, TRPM7 is also a target to be used for treating cancer. In addition, overexpression of these channels may serve as novel markers for carcinogenic cells or tumors.

Fig. 6D shows the participation of oxidative stress-modulated TRPM ion channels in some types of cancer.

8. Diabetes, metabolic disorders and bone disease

To study the role played by TRPM2 in pancreatic β-cell physiology, experiments in TRPM2-KO mice were performed [40]. In these mice, renal clearance of glucose was impaired. Additionally, insulin level in the bloodstream was reduced in the TRPM2-KO mice [40], suggesting that inhibiting TRPM2 activity generates and potentiates the loss of glycemic control. TRPM2 has been connected to the insulin secretion of pancreatic β-cells [38–40,146] and the downregulation of TRPM2 expression in rat insulinoma provided resistance to H_2O_2-induced cell death in comparison to control experiments [30,61]. Therefore, a case–control study was performed to assess the association of TRPM2 mutations with type II diabetes mellitus. However, this study showed no association between the tested TRPM2 mutants and diabetes. However, further analyses are required to explore additional cases as well as TRPM2 polymorphism [147].

Additionally, glucose-induced insulin secretion is abolished by the inhibition of TRPM4 expression in rat pancreatic β-cells, most likely because of the control of intracellular Ca^{2+} signaling [74,148]. Nonetheless, TRPM4-KO mice show normal glucose clearance and insulin secretion [149]. Further studies are required to resolve that discrepancy.

The downregulation of TRPM7, as well as its homologue TRPM6, was found in an animal model of inherited hypomagnesemia, suggesting that these alterations at the channel level were responsible for the development of the pathology [150]. Patients with autosomal dominant familial hypomagnesemia exhibit mutations in the TRPM6 gene [151,152]. Because TRPM7 is phylogenetically close to TRPM6, TRPM7 may also contribute to hypomagnesemia. Further experiments are required to confirm that hypothesis.

Silencing the TRPM7 channel expression diminished the magnesium starvation-induced cadmium uptake in osteoblasts [101]. Because cadmium exposure causes osteoporosis by disrupting bone metabolism, this finding suggests that, during a magnesium-depletion condition, TRPM7 becomes a key factor in promoting cadmium-induced osteoporosis.

This section is schematized in the Fig. 6E.

9. Concluding remarks

Although ion channel function is essential for organism viability, changes in or the absence of those functions are decisive in the initiation and progression of several human pathologies, known as channelopathies. Channelopathies most likely explain why ion channels are well-known targets of ancient and modern pharmacology. Most drugs actually in use are based on blocking or activating ion channels. Thus, it is not surprising that ion channels are a popular topic in clinical research.

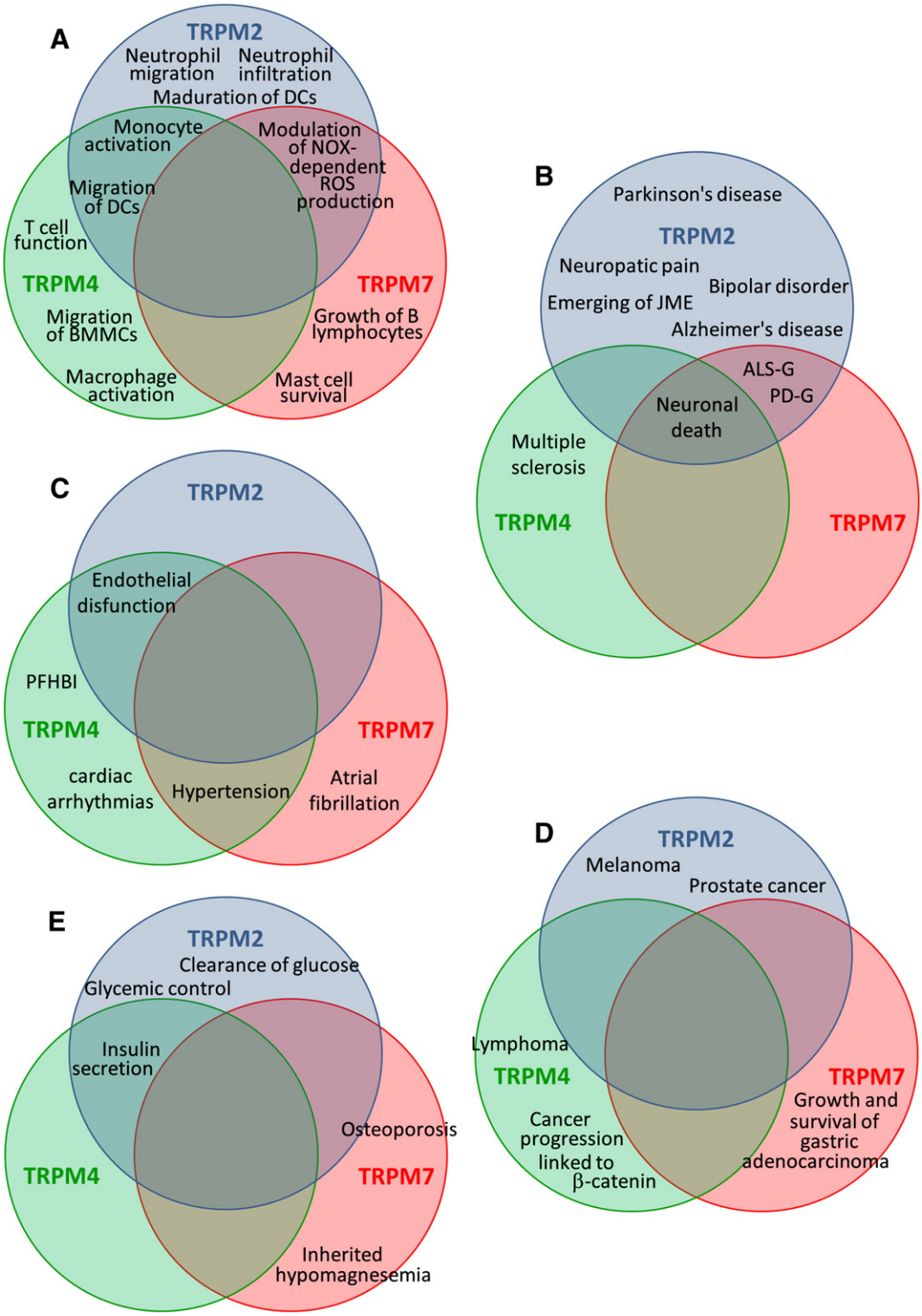

Fig. 6. Diagram of the (A) inflammatory response and immune system activation, (B) neurodegenerative diseases and neurological disorders induced, (C) cardiac diseases and vascular dysfunction, (D) cancer, (E) diabetes, metabolic disorders and bone disease induced by the oxidative stress-modulated TRPM ion channels, TRPM2 (blue), TRPM4 (green) and TRPM7 (red). NOX: NAD(P)H oxidase; DCs: dendritic cells; BMMCs: bone marrow-derived mast cells; ROS: reactive oxygen species; NOX: NAD(P)H oxidase; JME: Juvenile myoclonic epilepsy; ALS-G: Guamanian amyotrophic lateral sclerosis; PD-G: Parkinson-derived dementia; PFHBI: progressive familial heart block type I.

ROS cause nonspecific and random modifications in several cellular macromolecules, such as DNA, lipids and proteins, with the subsequent cellular malfunction. However, substantial evidence indicates that ROS itself and, principally, the ROS-induced modification of cellular molecules act in specific processes, such as signal transduction, molecule expression, and function regulation. ROS modification in proteins appears to exert a more specific effect on cell physiology. Additionally, these ROS-modified proteins are responsible for specific pathologies and syndromes. Therefore, therapeutic interventions on these ROS-modified proteins appear to be an effective clinical tool.

Similarly, the combination of oxidative stress and oxidant-modulated ion channels is critical in pathologies, which results in a novel paradigm in pathology. Advances in basic and clinical research will demonstrate whether these channels are useful for therapeutic interventions that improve the outcome of several human diseases.

Conflict of interest

None declared.

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