Transient receptor potential melastatin-2 channel and inflammation

H Vivanco-Cid, G Mellado-Sánchez, A Sumoza-Toledo*}

Abstract

Introduction

Inflammation is an early mechanism of the immune system to eliminate pathogens and to repair damaged tissue. However, unregulated and persistent inflammation can lead to chronic inflammatory diseases. The transient receptor potential melastatin-2 (TRPM2) channel, a calcium (Ca^{2+})-permeable channel containing intracellular adenosine diphosphoribose pyrophosphohydrolase activity, has recently been identified as a critical molecular mechanism in reactive oxygen species (ROS)-induced inflammatory process, and thereby, emerged as a potential target for therapeutic intervention. Adenosine diphosphoribose (ADPR) binding to TRPM2 Nudix-like domain (or NUDT9 homology domain) results in channel pore opening allowing lysosomal Ca^{2+} release and Ca^{2+} influx into the cells. Ca^{2+} influx via TRPM2 controls ROS induced nuclear translocation of nuclear factor-kappa B (NF-kB) and C-X-C motif chemokine 2 (CXCL2) production in monocytes during inflammation in a chronic experimental colitis model. Moreover, TRPM2 deficient dendritic cells show defective Ca^{2+} signals and chemotaxis towards C-X-C motif chemokine 12 (CXCL12) and chemokine C-C motif ligand 21 (CCL-21) while TRPM2−/− mice are also more susceptible to Listeria monocytogenes infection. In contrast, TRPM2 is not required for airway inflammation in ovalbumin (OVA)-induced allergic asthma and in chronic obstructive pulmonary disease in mice. Consequently, TRPM2 appears to play a role in chronic inflammation and might not participate in acute inflammatory responses. This review discusses the TRPM2 channel and inflammation.

Conclusion

Although the recent findings have advanced the understanding of the role of this protein in the context of the immune system, future work will focus on signalling pathways involved in the activation of TRPM2 in immune cells and to distinguish a differential role of TRPM2 in chronic inflammation and acute inflammation.

Introduction

Inflammation is both a mechanism of host defence and a repair mechanism of damaged tissue, generally categorised as acute and chronic inflammation. The acute inflammation is an early mechanism during antigen containment by immune cells and repairation of damaged tissue. It is characterised by the activation of resident cells [mast cells, macrophages, dendritic cells (DCs), endothelial cells] and by the infiltration of polymorphonuclear neutrophils into the damaged tissue. It is also characterised by high levels of innate immune cytokines and chemokines, such as tumour necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-12 and IL-8, granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF), respectively. In contrast, chronic inflammation is a persistent inflammatory response characterised by infiltration of mononuclear cells [macrophages, natural killer (NK) cells, and lymphocytes] and granulocytes (eosinophils and mast cells), macrophages and lymphocytes being the major components in the infiltrate. Main pro-inflammatory molecules present in chronic inflammatory responses are reactive oxygen species ROS, reactive nitrogen species (RNS), IL-2, IL-4, IL-5, IL-7, IL-13, IL-9, IL-10, IL-12, IL-17, IL-21, interferon (IFN)-γ, transforming growth factor (TGF)-β, and TNF-β. Interestingly, some cytokines, such as TNF-α, IL-1 and IL-6, can significantly contribute to both acute and chronic inflammations. Chronic inflammatory conditions can lead to local and systemic alterations, such as, progressive destruction of tissues, tissue remodelling, fibrosis, systemic inflammation, multi-organ failure, cancer development and death.

Main signalling pathways involved in both acute and chronic inflammations include the mitogen-activated protein kinase (MAPK), NF-κB, Janus tyrosine kinase-signal transducer and activator of transcription (JAK/STAT), and calcineurin/nuclear factor of activated T cells (NFAT). MAPKs are involved in signal transduction of different cytokines, response to microbial components, IFNs, colony-stimulating factors (CSFs), hormones and environmental stress signals. However, NF-κB has been found to be the most important regulator for both the inflammation responses. The NF-κB family consists of five members: v-rel avian reticuloendotheliosis viral oncogene homolog (c-REL), REL homolog A (REL-a; p65; NF-κB), REL homolog B-24 (REL-b24), NF-k (p50; p105), and NF-κB2 (p52; p100). The heterodimer of p50 and p65 is the most common activating form in inflammatory responses. NF-κB is activated by a diverse set of
Critical review

subfamily, share this dual function, although they present kinase activities. Recent studies on the TRPM2 channel have shown a regulatory role of this protein in migration and cytokine production in monocytes, neutrophils, and DCs. TRPM2 has also recently been identified as a critical molecular mechanism in the ROS-induced inflammatory process. Nevertheless, the physiological role of TRPM2 is not currently well understood. In this review, we will discuss recent findings that suggest a differential role of TRPM2 in acute inflammation and chronic inflammation.

Discussion

The authors have referenced some of their own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution

Figure 1: TRPM2 protein structure. (A) TRPM2 protein. The channel's N-terminal has four homologous regions (MHR), followed by six transmembrane segments (TM: S1–S6). The pore-forming loop domain is located between S5 and S6. The C-terminus contains a TRP box and a coil–coil domain (CC), and a C-terminal ADPR pyrophosphatase domain containing an ADPR pyrophosphatase enzymatic domain (Figure 1). This property of TRPM2 to function as a channel and as an enzyme classifies it as "chanzyme". Two other channels, TRPM6 and TRPM7, which are also the members of the TRP superfamily, melastatin

Ca^{2+} release from intracellular stores and Ca^{2+} entry via plasma membrane Ca^{2+} channels are essential mechanisms for the activation and functioning of immune cells. Therefore, they may regulate the immune response, including inflammation. TRPM2 (previously known as LTRPC2 or TRPC7) is a Ca^{2+}-permeable channel containing an ADPR pyrophosphatase enzymatic domain (Figure 1). This property of TRPM2 to function as a channel and as an enzyme classifies it as "chanzyme". Two other channels, TRPM6 and TRPM7, which are also the members of the TRP superfamily, melastatin

For citation purposes: Vivanco-Cid H, Mellado-Sánchez G, Sumoza-Toledo A. Transient receptor potential melastatin-2 channel and inflammation. OA Inflammation 2013 Nov 01;1(2):12.
in which they were performed. Animal care was in accordance with the institution guidelines.

TRPM2 channel

TRPM2 is a TRP-related protein of approximately 170 kDa, expressed in the plasma membrane and lysosomal membrane of several cells, including immune cells. The N-terminus, which is oriented towards the cytoplasm, comprises four melanatin homologous domains (MDH) and a calmodulin (CaM)-biding IQ-like motif. TRPM2 also contains six transmembrane segments (S1-S6), with a loop domain located between S5 and S6, which is involved in the formation of the channel pore. Meanwhile, cytoplasmic-oriented TRPM2 C-terminus consists of a TRP box, a coil-coil domain, which has been suggested to be critical for TRPM2 homo-tetrameric assembly, and a Nudix-like domain (or NUDT9 homology domain), which binds with high specificity and hydrolyses ADPR to ribose 5-phosphate and adenosine monophosphate (AMP) (Figure 1).

To form a non-selective cation channel, TRPM2 proteins typically assemble into homotetramers. Binding of ADPR to the TRPM2 Nudix-like domain, in synergy with Ca²⁺, opens the TRPM2 ion channel pore allowing the permeation, mainly, of sodium (Na⁺) and calcium (Ca²⁺), as well as potassium (K⁺) and caesium (Cs⁺) into the cell (Figure 1). In addition to Ca²⁺, cyclic ADPR (cADPR), hydrogen peroxide (H₂O₂) and nicotinic acid adenine dinucleotide phosphate (NAADP) may directly or indirectly facilitate TRPM2 gating by ADPR. In contrast, AMP and protons regulate it negatively.

Recently, it has also been suggested that expression of TRPM2 isoforms might regulate its cellular function. Thus, TRPM2 ΔC, which lacks 34 residues (T1292–L1325) in the C-terminus, fails to respond to ADPR, but can still be activated by H₂O₂. Other isoforms, striatum short protein (SSF)-TRPM2, which consists of TRPM2 transmembrane segments and the C-terminus, also retain H₂O₂-induced activity. In contrast, TRPM2 ΔN, which is missing 20 residues (K538–Q557) in the N-terminus, does not respond to H₂O₂. In addition, a short version of TRPM2 (TRPM2-S), consisting of only the N-terminus and S1-S2, may function as a dominant negative inhibitor of TRPM2 activity. Interestingly, variants of TRPM2 (melanoma-enriched antisense TRPM2 transcript and a tumour-enriched TRPM2 transcript) have been detected in tumour cells.

TRPM2 signalling in immune cells

Expression of TRPM2 has been described so far in the plasma membrane of neutrophils, T cells and monocytes, and in lysosomes of DCs. On the other hand, immune cells may produce ADPR, which is considered to be the main activating molecule of TRPM2, via Cluster of Differentiation (CD) 38 (CD38) and CD157 and by activation of the poly(ADPR)-polymerase/poly(ADP-ribose) glycohydrolase (PARP/PARG) pathway during DNA repair, replication and transcription. However, mechanisms that link these pathways to TRPM2 activation are not yet clearly understood. Ectoenzymes, CD38 and CD157, use β-Nicotinamide adenine dinucleotide (b-NAD⁺) as a substrate to catalyse the production of ADPR, cADPR, and NAADP; however, these metabolites are produced extracellularly and it is still not known how they might cross the plasma membrane and act on the cytosolic Nudix domain of TRPM2. Interestingly, CD38 knockout neutrophils show defects in chemotaxis linked to an impaired Ca²⁺ entry, similar to TRPM2–/– neutrophils. These findings were also confirmed in TRPM2−/− mouse monocytes, which were unable to mobilise extracellular Ca²⁺ in response to H₂O₂ and to produce CXCL2 cytokine. These DCs express TRPM2 only in lysosomes. In DCs, lysosomal TRPM2 functions as a Ca²⁺ release channel, although it also indirectly regulates Ca²⁺ entry when immature and mature DCs are stimulated with chemokines CXCL12 and CCL-19. Immature and mature TRPM2−/− DCs also show impaired chemotaxis towards CXCL12 and CCL-19, respectively. Furthermore, a lower percentage of the DC population from TRPM2−/− mice expresses costimulatory molecules, such as CD80, CD86, major histocompatibility cluster-II (MHC-II) and CD83 upon cellular activation with TNF-α and Cytosine-phosphate-Guanine nucleotides ( CpG). However, the signalling pathways involved are unknown.

Role of TRPM2 in acute and chronic inflammation processes

The TRPM2 channel has been associated to different pathological conditions, including bipolar disorder, diabetes, chronic colitis, oxidative stress, ischaemia and cancer. However, the molecular mechanisms of TRPM2 in their plasma membrane and consequently Ca²⁺ enters the cell, contributing to activation of Ca²⁺-dependent tyrosine kinase 2 (PYK2), amplification of extracellular signal-regulated kinase (ERK) signalling via RasGTPase, translocation of NF-κB and production of CXCL8 cytokine. These findings were also confirmed in TRPM2−/− mouse monocytes, which were unable to mobilise extracellular Ca²⁺ in response to H₂O₂ and to produce CXCL2 cytokine. These findings were also confirmed in TRPM2−/− mouse monocytes, which were unable to mobilise extracellular Ca²⁺ in response to H₂O₂ and to produce CXCL2 cytokine. These findings were also confirmed in TRPM2−/− mouse monocytes, which were unable to mobilise extracellular Ca²⁺ in response to H₂O₂ and to produce CXCL2 cytokine.
that lead to activation of TRPM2 and therefore development of these diseases are not clearly understood. Yamamoto et al., using a dextran sulphate sodium (DSS)-induced colitis inflammation model, demonstrated that TRPM2 controls the severity of inflammation and ulceration of the colon by affecting the production of IFN-Y, IL-12, CXCL2 and subsequent infiltration of neutrophils20. Interestingly, TRPM2–/– mice are particularly susceptible to infection with Listeria monocytogenes due an impaired production of IFN-Y and IL-1221. Furthermore, in a TRPM2–/– mouse model of sciatic nerve injury-induced neuropathic pain, the neutrophil infiltration was diminished as a consequence of reduction in CXCL2 chemokine production22,23. These findings indicate the role of TRPM2 in regulating IFN-γ, IL-12, CXCL2 expression. TRPM2 also plays a protective role in a lipopolysaccharide (LPS)-induced lung inflammation mouse model by preventing ROS production in neutrophils24,25. Contrariwise, recent studies on chronic obstructive pulmonary disease in mice exposed to ozone, LPS and tobacco smoke26,27 and OVA-induced mouse allergic asthma showed no role of TRPM2 in airway inflammation28,29. These findings are highly suggestive of a role of TRPM2 in chronic inflammation, but not in acute inflammation, probably by regulating the production of cytokines.

**Conclusion**

The TRPM2 channel is a versatile channel, which can regulate Ca2+ entry and Ca2+ release. It is widely expressed in cells, including immune cells, in which the regulation of intracellular Ca2+ is very important for activation, migration and function. Although recent findings have advanced the understanding of the role of this protein in the context of the immune system, future work will focus on signalling pathways involved in the activation of TRPM2 in immune cells and on distinguishing a differential role of TRPM2 in chronic inflammation and acute inflammation.

**Abbreviations list**

ADPR, adenosine diphosphate ribose; AMP, adenosine monophosphate; Ca2+, calcium; CADPR, cyclic ADPR; CaM, calmodulin; CD, Cluster of differentiation; CSF, colony-stimulating factor; CpG, Cytosine-phosphate-Guanine nucleotides; CXCL, C-X-C motif chemokine; CC, CCL; chemokine C-C motif ligand; DAMP, damage-associated molecular pattern; DC, dendritic cell; DSS, dextran sulphate sodium; ERK, extracellular signal-regulated kinase; FMLP, formyl-Methionyl-Leucyl-Phenylalanine; FoxP, forkhead box P3; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GATA-3; guanine adenine thymine adenine biding protein-3; H2O2, hydrogen peroxide; IFN, interferon; IL, interleukin; JAK/STAT, Janus tyrosine kinase-signal transducer and activator of transcription; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MDH, melastatin homologous domain; MHC-II, major histocompatibility cluster–II; NAADP, nicotinic acid dinucleotide phosphate; b-NAD6, b-Nicotinamide adenine dinucleotide; NFAT, nuclear factor of activated T cells; NF-kB, nuclear factor kappa B; NK, natural killer; NUDT, Nudix-like domain; PAMP, pathogen-associated molecular pattern; PYK2, tyrosine kinase 2; REL, v-rel avian reticuloendotheliosis viral oncogene homolog; ROS, reactive oxygen species; RNS, reactive nitrogen species; ROR-γ, nuclear receptor ROR-gamma; T-bet, transcription factor T-bet;Th, helper T TGF, transforming growth factor; Tregs, regulatory T cell; TLR, Toll-like receptors; TNF, tumour necrosis factor; TRPM2, transient receptor potential melastatin-2.

**References**


Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

For citation purposes: Vivanco-Cid H, Mellado-Sánchez G, Sumoza-Toledo A. Transient receptor potential melastatin-2 channel and inflammation. OA Inflammation 2013 Nov 01;1(2):12.

Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)

For citation purposes: Vivanco-Cid H, Mellado-Sánchez G, Sumoza-Toledo A. Transient receptor potential melastatin-2 channel and inflammation. OA Inflammation 2013 Nov 01;1(2):12.