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Review

TRPM channels as potential therapeutic targets against pro-inflammatory diseases

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ABSTRACT

The immune system protects our body against foreign pathogens. However, if it overshoots or turns against itself, pro-inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, or diabetes develop. Ions, the most basic signaling molecules, shape intracellular signaling cascades resulting in immune cell activation and subsequent immune responses. Mutations in ion channels required for calcium signaling result in human immunodeficiencies and highlight those ion channels as valued targets for therapies against pro-inflammatory diseases. Signaling pathways regulated by melastatin-like transient receptor potential (TRPM) cation channels also play crucial roles in calcium signaling and leukocyte physiology, affecting phagocytosis, degranulation, chemokine and cytokine expression, chemotaxis and invasion, as well as lymphocyte development and proliferation. Therefore, this review discusses their regulation, possible interactions and whether they can be exploited as targets for therapeutic approaches to pro-inflammatory diseases.

Contents

1. Cation signaling in innate and adaptive immunity

Human immunodeficiencies resulting from disrupted calcium (Ca^{2+}) and magnesium (Mg^{2+}) entry pathways have highlighted the importance of cationic signaling in immune cell responses [1,2]. Complex intracellular signaling cascades, depending on cations as basic signaling molecules, are required for immune cell activation and subsequent immune responses [3]. Upon T cell receptor (TCR) activation via antigen presenting cells (APCs), such as dendritic cells, macrophages and B lymphocytes, phospholipase Cγ1 (PLCγ1) is phosphorylated and in turn catalyzes the hydrolysis of phosphatidylinositol (4,5) biphosphate (PIP_2) into diacylglycerol (DAG) and inositol (1,4,5) triphosphate (IP_3). Subsequently, IP_3 triggers Ca^{2+}-release from the ER Ca^{2+} store via the IP_3 receptor (IP_3R) and DAG, in conjunction with Ca^{2+}, activates protein kinase C (PKC). Upon depletion of luminal ER Ca^{2+}, the stromal interaction molecule (STIM) translocates to the plasma membrane (PM) and triggers store-operated Ca^{2+} entry (SOCE) via CRAC (Calcium Release Activated Calcium) channels [4,5], which is one of the best-studied initial events in leukocyte activation [2,6,7]. However, the role of other cation channels in immune cell function is far less

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understood, although they might be of similar importance in shaping effective immune responses.

For innate leukocytes, such as monocytes, macrophages, dendritic cells, granulocytes and mast cells, Ca^{2+} signals are essential for their activation, initiating chemotaxis, phagocytosis, exocytosis and secretion [8–10]. Nonselective inhibition of Ca^{2+} signaling strongly impairs many effector functions of macrophages and dendritic cells, including phagocytosis, inflammasome activation, and priming of T cells [11]. However, murine macrophages and dendritic cells with complete inhibition of SOCE due to conditional deletion of *Stim1* and *Stim2* genes showed no major functional defects. Their differentiation, phagocytosis, cytokine production, inflammasome activation, and their ability to activate T cells was preserved, indicating that SOCE is dispensable for many effector functions of macrophages and dendritic cells and that other Ca^{2+} entry pathways are required for innate immunity [11]. Murine and human neutrophils with deletions in *Stim* or CRAC channel (*Orai/CRACM*) genes showed reduced chemotactic signaling, but phagocytosis was mostly unaffected. Several candidates might compensate the lack of STIM and CRAC channels as phagocytes possess a large variety of Ca^{2+} signaling molecules at the ER, in acidic Ca^{2+} stores, such as lysosomes, and at the PM, including melastatin-like transient receptor potential (TRPM) channels (Fig. 1) [12]. Interestingly, genetic ablation of *Stim1* or *Orai1/CRACM1* genes in mast cells strongly affects their effector functions, including degranulation and exocytosis, as well as in *in vivo* models of anaphylactic and allergic reactions, respectively [13,14]. Similarly, TRP proteins play an essential role in Ca^{2+} signaling and activation of mast cells (Fig. 2) [15,16].

Initiated by the innate immune system, lymphocyte signaling affects long lasting immune responses of adaptive immunity. In lymphocytes sustained elevation of intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$) is essential for translocation of NFAT (nuclear factor of activated T cell), subsequent IL-2 expression, clonal expansion and differentiation into distinct effector T cell subsets [17–19]. In addition to CRAC channels, ion channels such as potassium channels, i.e. Kv1.3 and $IK_{Ca}1$, chloride channels, i.e. Cl_{swell} and TRPM cation channels, i.e. TRPM4, constitute a network, which crucially impacts T cell activation by regulating the initiation, intensity, and duration of Ca^{2+} signals via shaping a cell's membrane potential (Fig. 3) [3,20,21]. Also certain TRP channels, such as members from the canonical TRPC family, TRPC1 and TRPC3 as well as the vanilloid TRPV6, have been proposed to function as store-operated Ca^{2+} channels and to interact with STIM1 and CRAC proteins [22,23]. However, TRPC channels are no longer considered part of CRAC channels. Despite this, they may be essential for Ca^{2+} signaling and lymphocyte activation and differentiation [24,25]. In human immunodeficiency the Mg^{2+} transporter MagT1 has been shown to be essential for T cell activation. The Mg^{2+} uptake via MagT1 triggers the activation of PLCγ1 followed by SOCE, suggesting a second messenger role for Mg^{2+} [1]. The contribution of CRAC channels, potassium and chloride channels to SOCE as well as P2X receptors, TRPC/TRPV and voltage-dependent Ca_v channels to Ca^{2+} signaling in immune cells has been discussed in detail in recent reviews [3,24–26]. Therefore, this review will focus on the role of TRPM channels in the immune system and whether they can be exploited as potential pharmacological targets against pro-inflammatory diseases.

2. Expression of TRPM proteins in immune organs and leukocytes

The mammalian transient receptor potential (TRP) superfamily of nonselective cation channels can be divided into six subfamilies, TRPC ("canonical"), TRPM ("melastatin"), TRPV ("vanilloid"), TRPA ("ankyrin"), TRPP ("polycystin"), and TRPML ("mucolipin"). The TRPM subfamily comprises 8 members, named after its founding member, melastatin, TRPM1 [27]. They consist of six transmembrane segments (S1–S6) with a pore-forming loop between S5 and S6. The segments are flanked by four homologous regions (MHR) and a calmodulin binding IQ-like motif at the N-terminus, as well as a TRP box and a coiled–coil domain (CC) at the C-terminus [28]. TRPM channels are widely expressed in immune organs (Table 1) [28–30]. Murine *Trpm1*, for instance, showed specific expression in lymph nodes, thymus and spleen, but was not detected via RT-PCR in liver, or kidney [29]. A quantitative real-time PCR analysis revealed high relative expression levels of human *Trpm1* in bone marrow cells and macrophages. Interestingly, in the spleen no *Trpm1* expression was detected [30]. *Trpm2* was expressed in all organs except the skin and bone [29,30] and particularly high relative expression was observed in macrophages and peripheral blood mononuclear cells (PBMCs) [30]. *Trpm3* was weakly expressed in immune organs, but as immune organs represent a heterologous population of cells, the detection of *Trpm* genes could be due to expression in other cell types like epithelial cells. Indeed, when looking at the cellular level, *Trpm3* was not detected in immunocytes [29]. However, a recent study demonstrates TRPM3 surface expression in B cells and natural killer (NK) cells [31]. *Trpm4* and *Trpm7* are ubiquitously expressed [29,30]. *Trpm5* was detected in immune organs as well as in PBMCs and bone marrow cells and, at very low levels, in macrophages [29,30]. *Trpm6* was expressed in all organs except skin and bone. Although *Trpm8* mRNA was not detected in immune organs [29], its expression becomes evident due to studies linking it to mast cell activation and phagocytosis of macrophages [32–34]. This variability could be due to species related differences or due to varying expression patterns in differentially differentiated primary cells and cell lines.

3. TRPM channels in innate and adaptive immune cell signaling

3.1. TRPM1 in melanogenesis

TRPM1 (melastatin) is the founding member of the melastatin-like TRPM cation channel subfamily. Like most TRPs it is a non-selective cation channel highly permeable for Ca^{2+}, however, so far it has been difficult to measure functional TRPM1 channels [35,36]. A role for TRPM1 was first described in highly metastatic melanoma cells, where it was down-regulated [37]. Down-regulation of TRPM1 lead to a decrease of intracellular Ca^{2+} resulting in less melanin pigmentation [38]. The decrease of TRPM1 in melanoma cells has been linked to the aggressiveness of melanoma, suggesting TRPM1 as useful prognostic marker for metastatis [37,39]. TRPM1 inhibition by NED-180 resulted in inhibition of melanogenesis, thus suggesting TRPM1 as promising therapeutic target [40].

The channel encoded by the *trp* gene, the first identified TRP protein, is known to mediate *Drosophila* light responses [41]. Recent studies finally revealed that TRPM1 is a visual transduction channel in retinal ON-bipolar cells, neuronal cell types of the retina [35,42,43]. There, TRPM1 plays a role in the pathway crucial for vision at low light intensities. Mutations in the TRPM1 gene in humans lead to congenital stationary night blindness [44]. Like for many TRP channels, phosphatidylinositol-4,5 bisphosphate (PIP_2) has been identified as a potential regulator of TRPM1, although the mechanism of the regulation still remains unclear [45]. In addition, it was found that activation of PKCα potentiates TRPM1 currents, while intracellular Mg^{2+} inhibited them [46]. Although TRPM1 expression has been detected in B and T lymphocytes as well as in mast cells [29], nothing is known about its role in leukocyte phys-