Regulation of Murine Dendritic Cell Functions by Calcium Channels

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Abstract

Dendritic Cells (DCs) are highly potent Antigen-Presenting Cells (APCs) that have a key role in mediating tolerance or immunity to self and non-self antigens. In their immature stage DCs are highly phagocytic and undergo a maturation process after taking up an antigen. DC maturation is characterized by activation of mechanisms of antigen presentation, increased expression of Major Histocompatibility Complex (MHC) class II and co-stimulatory molecules in the plasma membrane, and secretion of cytokines and chemokines. Despite the fact that the role of calcium (Ca^{2+}) in DC function has been clearly established, regulation of Ca^{2+} signals in these cells is not well known. However, recently it has been demonstrated that functional capacitative Ca^{2+} release-activated Ca^{2+} (CRAC), Transient Receptor Potential Melastatin-2(TRPM2) and TRP Vanilloid- 1 (TRPV1) channels are critical for mouse DC maturation and migration. Also, Ryanodine Receptor-1 (RyR1) signaling activated by L-type Ca^{2+} channel CaV1.2 cause rapid MHC-II expression in the plasma membrane of DCs. The understanding of the regulation of Ca^{2+} signals in DCs is essential, to potentially modulate DC functions in disease processes. Therefore, in this review, we discuss recent studies on the expression and roles of Ca^{2+} channels in DC biology and function.

Keywords: Calcium; Dendritic cells; Ion channels; CRAC; TRPM2; TRPV1; RyR

Introduction

Dendritic cells (DCs) are Antigen-Presenting Cells (APCs) that play a critical role in the regulation of both: innate and adaptive immune responses. Initially, DCs were described by Ralph Steinman in 1973 [1], as a different immune cell population in the spleen and lymph nodes of mice. DCs are the only APCs that have the ability to induce a primary immune response in naïve T lymphocytes, and therefore they are considered the most potent APCs, influencing the type and quality of the response [2]. DCs can exist in two main states: In a steady state immature Dendritic Cells (iDCs) and fully mature DCs (mDCs). The distinction between immature and mature DCs is based on phenotypic markers and biological functions [3]. iDCs lack or have low levels of several important accessory molecules that mediate binding and stimulation of T cells, such as CD40, CD54, CD58, CD80, CD83 and CD86. They also express high levels of intracellular Major Histocompatibility Complex (MHC) class II molecules. On the cell surface, iDCs express high levels of chemokine receptors such as CCR1, CCR5, and CCR6. Functionally, iDCs are characterized by high endocytic activity and low T-cell stimulation potential [4-7]. Phenotypic maturation is characterized by down-regulation of the capacity to capture antigens and up regulation of antigen processing and presentation functions. The mDCs phenotype is characterized by expression of high levels on the surface of MHC II, CCR7, CD40, CD54, CD80, CD83, CD86, CD58 and low expression of CCR1, CCR5, CCR6 [4-7]. DCs are also able to interact with other cells besides T cells, such as Natural Killer (NK) cells, neutrophils, and epithelial cells [8-10]. Other critical roles of DCs in immunity are the maintenance of B cell function, the establishment of immunological memory, and the maintenance of peripheral tolerance [11].

DC Subsets

DCs are widely distributed in all tissues, especially in those that provide an environmental interface, such as the skin and mucosal tissues. Similar to other immune cells, DCs are divided in subsets, which have been shown to possess a differential ontogeny, morphology, phenotype, transcriptional programs and functions [12]. In mice, DCs can be subdivided into CD8+ CD11b+ and CD8- CD11b+ conventional DCs (cDCs), a lineage originated from a myeloid progenitor in the bone marrow. cDCs characteristically express high levels of MHC class II and the integrin CD11c, but not B220 marker [13-16]. cDC subsets are activated by microbial products through cell surface Toll- like Receptors (TLRs) to produce inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-12, and tumor necrosis factor-alpha (TNF-α) and they are specialized in the activation of CD8+ and CD4+ T cells [17]. They have a predominant role in MHC- II presentation and immunological tolerance, inducing clonal deletion of auto reactive T cell or Treg differentiation [18,19]. CD8+ CD11b+ DCs are specialized in the induction of CD8+ T cell immunity. They are the main source of IL-12 and IL- 15 [18], two cytokines involved in the differentiation of cytotoxic CD8+ T cells and have the ability to prime CD8+ T cell responses in a cross-presentation dependent mechanism [20]. CD8- CD11b+cDCs can sense pathogens and migrate from non-lymphoid tissues to regional lymph nodes charged with self and foreign antigens.

Other cDCs subsets include migratory CD103+ CD11b- DCs, CD103- CD11b+ DCs, and Langerhans Cells (LCs), which are abundant in the intestinal mucosa and skin [21-24]. DCs can also be originated from a lymphoid progenitor. Plasmacytoid DCs (pDCs) are the prominent subset of this group, which phenotypically express CD8α+ CD11b- B220+ DC SING+ [25,26]. The other pDCs specific surface marker is the murine Siglec H [27]. pDCs are a specialized population that have the ability to produce very large amounts of interferon alpha/beta (IFN-α/β) upon activation and a limited ability to prime naïve CD4+ and CD8+ T cells. They are an important DCs subset in viral and anti-tumoral immunity [26]. Other DCs subsets include *in vitro* or *in vivo* inflammatory or infection-derived DCs, which develop from monocytes in response to stimulation such as Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), IL-4 and TNF-α [28]. A summary of DC subsets is showed in Table 1.

Early studies using Ca^{2+} ionophores and $Ca2^+$ chelators have shown that Ca^{2+} signals may trigger maturation and functional properties of DCs [29-31]. Intracellular Ca^{2+} ions are crucial second messengers to initiate signaling pathways for fundamental cellular functions, such as cell cycle, survival, apoptosis, migration, and gene expression[32,33]. Regulation of intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$; ~100 nM) involves both Ca^{2+} entry from the extracellular space and Ca^{2+} release from intracellular stores, such as calciosomes, Endoplasmic Reticulum (ER), lysosomes, or mitochondria, by specialized pumps and ion channels [32-34]. Although $[Ca^{2+}]_i$ increase triggers signaling pathways in the cell, the exquisite spatial and temporal organization of Ca^{2+} oscillations, waves and sparks might also provide a code for selective activation of signaling pathways and their duration. For example, a short $[Ca^{2+}]_i$ increase is observed in lymphocytes during immunological synapse, release of lytic granules, and cytotoxicity. In contrast, prolonged $[Ca^{2+}]_i$ increase regulates cytokine production, cell differentiation, effector
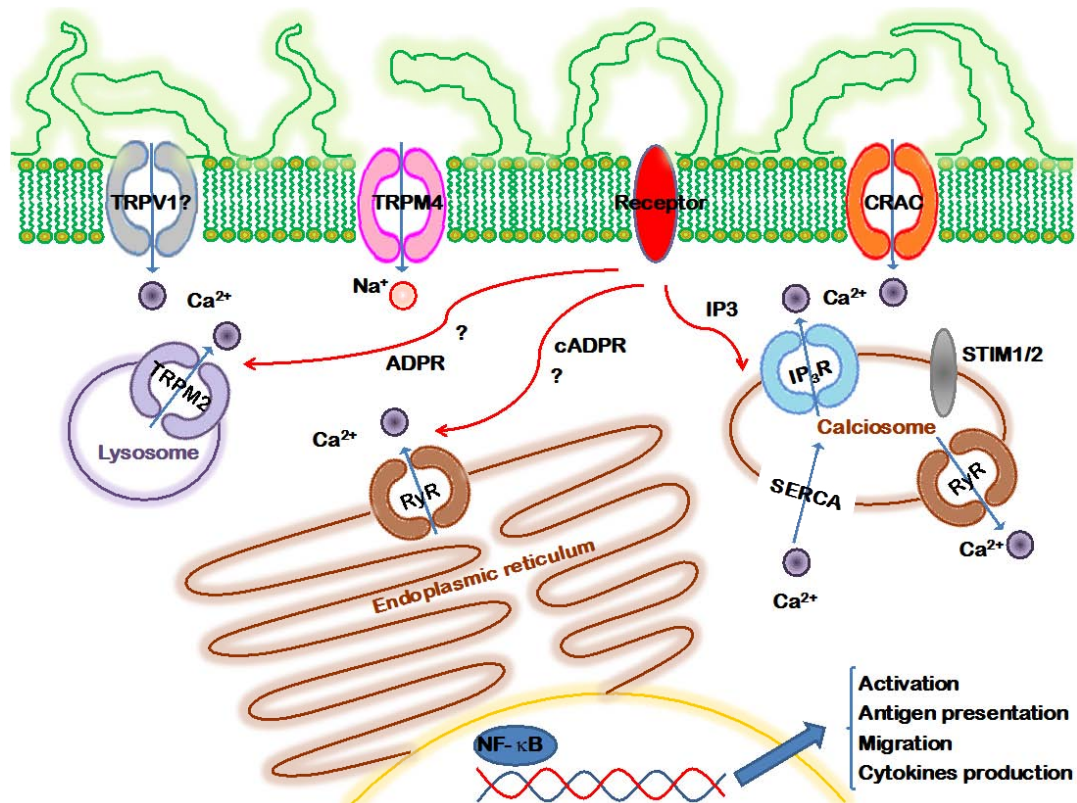
Figure 1: Calcium channels in DCs: Extracellular signals (chemokines, cytokines, microbial peptides, etc) are recognized by DCs by means of G protein-coupled receptors or receptor protein tyrosine kinases, activating the formation of 1,4,5-triphosphate (IP3) that in turn binds to IP3 receptors in the ER and calciosomes, causing Ca^{2+} release. Decrease in the luminal Ca^{2+} in the ER is detected by the Stromal Interaction Molecule 1/2 (STIM1/2) resulting in the activation of Capacitative Ca^{2+} Release-Activated Ca^{2+} (CRAC) channels, allowing Ca^{2+} influx across the plasma membrane. Chemokines also activate Transient Receptor Potential Melastatin- 2(TRPM2) channels in DC lysosomes. The Ca^{2+} signals activate transcription factors such as Nuclear Factor of Activated T cells (NFAT) or Nuclear Factor-κB (NF-κB) for gene expression. TRPM4, a Ca^{2+} activated TRP channel that allows Na^+ into the cell is expressed in the plasma membrane of DCs and indirectly regulates DC functions by decreasing the driving force for Ca^{2+} entry through CRAC channels. DCs also express TRP Vanilloid-1 (TRPV1) and Ryanodine receptor (RyR) channels but their functions are still not clear.

Table 1: Dendritic cell subsets.

DC subsets	CD8α	CD103	CD205	CD11b	B220 or CD45RA	DC-SING	Langerin (CD207)	MHC class II	CD11c
pDCs	+	-	-	-	+	++	-	+	+
CD8α+ DCs	+	low	+	+	-	-	+/-	++	+++
CD8α-CD11b+ DCs	-	+/-	+	+	-	ND	-	++	+++
CD103+ DCs	-	+	++	-	-	-	+	++	++
Lung Intestine	-	+	-	+	-	-	-	+	++
Langerhans cells	-	-	++	+	-	-	++	++	++
Monocyte-derived inflammatory DCs	-	-	-	+	-	+	-	++	++

functions, etc. The present review addresses the role of Ca^{2+} channels in DC functions [33,35].

Ca^{2+} Release-Activated Ca^{2+} Channels (CRAC) in DC

The main mechanism for Ca^{2+} entry in immune cells, including DCs, is the Store-Operated Ca^{2+} Entry (SOCE). SOCE is activated by Ca^{2+} release from the intracellular stores and involves the activation of Capacitative Ca^{2+} Release-Activated Ca^{2+} (CRAC) channels in the plasma membrane (Figure 1) [34,36,37]. SOCE-mediated Ca^{2+} influx provides ions not only for signaling purposes, but also for ER and calciosomes store refilling. SOCE activation can be initiated by stimulation of G protein-coupled receptors or stimulation of receptor protein tyrosine kinases by external signals (cytokines, chemokines, bacterial peptides, etc), leading to activation of Phospholipase C (PLC) that in turn hydrolyzes phosphatidylinositol- 4,5- bisphosphate (PIP2) to release Inositol-1,4,5-triphosphate (IP3) and Diacylglycerol (DAG) [33,34].The subsequent binding of IP3 to IP3 receptors in the ER and calciosomes causes a rapid and transient Ca^{2+} release, raising the $[Ca^{2+}]_i$ (Figure 1). On the other hand, the decrease in the luminal Ca^{2+} in the ER is detected by the stromal interaction molecule 1/2 (STIM1, STIM2; Ca^{2+} sensors; Figure 1), resulting in its conformational change (oligomerization and aggregation) and activation of CRAC channels [33,34]. CRAC channels, which pore is formed by CRACM/Orai 1-3 proteins, then allow influx of extracellular Ca^{2+} across the plasma membrane (Figure 1). CRAC are highly Ca^{2+}-selective, low conductance channels with a characteristic inwardly rectifying current-voltage relationship [33,34]. Interestingly, Orai and STIM proteins may have different tissue distribution, selectivity and conductivity for Ca^{2+}.

As a result of $[Ca^{2+}]_i$ increase several signaling pathways and transcription factors are activated, such as the calmodulin-calcineurin pathway that activate the Nuclear Factor of Activated T cells (NFAT), the Ca^{2+}- dependent kinase-calmodulin (CaMK) pathway which activate the Cyclic-adenosine monophosphate-Responsive Element Binding protein (CREB), and the nuclear factor B (NFκB) pathway. Moreover, the DAG formed from PIP2 hydrolysis can activate the Protein kinase C pathway (PKC), and Ras-mitogen-activated protein kinase, which ultimately activate transcription factors such as Activating Protein-2 (AP-2) and NFκB [33,34].

Although the presence of CRAC currents and its role in DC maturation have previously been demonstrated in mouse DCs [36], it has only recently been shown that Orai2 and STIM2 are most abundant in DCs [38]. Furthermore, recruitment of Orai2 and STIM2 towards the immunological synapse has been observed during antigen presentation of DC to T lymphocytes [38]. Likewise, studies using CRAC blockers have shown that this channel plays an important role in DC maturation, cytokine production (TNF-α and IL-6) and chemotaxis [37]. DC maturation can be triggered *in vitro* by increasing $[Ca^{2+}]_i$ by stimulating them with peptidoglycan (PGN), CpG DNA, microbial products like Lipopolysaccharide (LPS) [39,40], or ionophores [29-31]. It has also been suggested that LPS, PGN and CpG induced activation of PLC γ2 [39], which in turn acts on PIP2 to produce IP3 that leads to Ca^{2+} release from intracellular stores; followed by CRAC channel activation (reviewed in [34]) causing the nuclear translocation of calcineurin-dependent NFAT factor and cytokine production, such as IL-2 [33,41]. On other hand, DC maturation with Ca^{2+} ionophoresis associated with NFκB activation, likely by activating Calcium/Calmodulin-dependent Kinase II (CaMKII), which inactivates NFκB-inhibiting molecule IkB similar to what has been shown in T cells [42].

In addition, DC chemotaxis depends on Ca^{2+} influx. DC chemotactic response to chemokines, including (C-X-C motif) ligand 12 (CXCL12) and (C-C motif) ligand 21 (CCL21), results in PLC activation, IP3 production, Ca^{2+} release from intracellular stores, and subsequent activation of CRAC channels and Ca^{2+} influx [31,40,43,44].

Transient Receptor Potential (TRP) Channel in DC

Our previous study has shown that lysosomal Ca^{2+} release through TRP Melastatin-2 (TRPM2) channel, the second member of the TRP melastatin-related channel family, plays an important role in DC maturation and chemotaxis (Figure 1) [40]. TRPM2 channel is expressed in DC only in lysosomes [40]. This channel is synergically activated by Adenosine Diphosphate Ribose (ADPR) and Ca^{2+}, and allows entry of sodium (Na^+), Ca^{2+}, potassium (K^+) and caesium (Cs^+) into the cytosol. In addition to Ca^{2+}, cyclic ADPR (cADPR), hydrogen peroxide (H_2O_2) and Nicotinic acid Adenine Dinucleotide Phosphate (NAADP) may directly or indirectly facilitate TRPM2 gating by ADPR [45]. DCs may produce ADPR by

means of CD38 activity, an ectoenzyme that use β-Nicotinamide Adenine Dinucleotide (β-NAD$^+$) as a substrate to catalyse the production of ADPR, cADPR, and NAADP, and by activation of the Poly(ADPR)-Polymerase/Poly(ADP-ribose) Glycohydrolase (PARP/PARG) pathway during DNA repair, replication and transcription [45]. DCs lacking TRPM2 channels express reduced levels of co stimulatory molecules, such as CD80, CD86, MHC-II and CD83, in the plasma membrane when they are stimulated with TNF-α and CpG DNA, than TRPM2 expressing-DCs [40]. They also show reduced Ca^{2+} signals in response to CXCL12 and CCL21, affecting the chemotaxis response towards these chemokines [40]. However, the mechanisms that link CD38 and PARP/PARG pathways to TRPM2 and to chemokine receptors are still not clearly understood.

DCs also express TRP Vanilloid-1 (TRPV1) protein in their plasma membrane, another non-selective Ca^{2+} channel of the TRP family, which is activated by capsaicin. But, there is controversial data on the expression and function of this channel in DCs. Earlier studies from Basu and Srivastava showed that extracellular Ca^{2+} influx via TRPV1 activation induces mouse DC maturation and provokes increase in the expression level of MHC class II and CD86 on the surface [46]. Conversely, O'Connell PJ et al. [47] did not detect TRPV1 transcripts and TRPV1 currents in bone marrow derived-mouse DCs. A recent study by Tóth BI et al. [48] shows molecular and functional expression of TRPV1 channels in monocyte derived-human DCs. Although DC stimulation with capsaicin induces Ca^{2+} mobilization, this reduces the expression level of maturation markers in DCs, such as CD83 and CCR7 [48]. On the other hand, TRPM4, a Ca^{2+}-activated TRP channel that allows Na$^+$ into the cell, indirectly regulates DC migration but not maturation by decreasing the driving force for Ca^{2+} entry through CRAC channels [43].

Ryanodine and Purinergic Receptors in DC

Ryanodine Receptor-1 (RyR1), a channel expressed in intracellular Ca^{2+} stores, is also expressed in DCs [49,50]. RyR1 signaling coupled with L-type Ca^{2+} channel CaV1.2, which has been also detected in DCs, cause rapid MHC class II expression in the plasma membrane of DCs [50]. Interestingly, RyRs are also activated by cADPR and NAADP$^+$, and might contribute through these pathways to DC maturation [44,51,52]. Finally, DCs express Purinergic Receptors (P2Rs), P2X (ligand-gated ion channels) and P2Y (G-protein coupled receptors) on their surface, such as P2X1, P2X4, and P2X7, and P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, and P2Y14, respectively. DC stimulation with Adenosine Triphosphate (ATP), a Damage-Associated Molecular Pattern (DAMP) molecule released by injured cells during inflammation and necrosis, or UTP results in characteristic Ca^{2+} signaling associated to P2X or P2Y, mainly P2X7 [53-57].

Concluding Remarks

Not much is known about Ca^{2+} channel expression and Ca^{2+} regulation in DCs. Recent studies have addressed the role of CRAC, TRPV1, TRPM2, RyR1 and CaV1.2 channels in DC maturation and migration. However, the mechanisms that lead to activation of these channels during DC function are not well

understood. Moreover, future studies still need to address which channels regulate Ca^{2+} signals during antigen presentation, immune synapse, apoptosis, and other DC functions. The meaning of Ca^{2+} oscillations, frequency and patterns are unknown, which might play an important role in establishing and/or maintaining immunological tolerance or immunity to self and non-self antigens.

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