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Ca^{2+} signaling in T-cell subsets with a focus on the role of Ca_v1 channels: possible implications in therapeutics

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The role of voltage-dependent calcium (Ca_v1) channels is prominent in excitable cells while store-operated calcium channels (SOCC) were considered as characteristic of non-excitable cells. Ca_v1 channels are implicated in excitation transcription. Store-operated calcium channels (SOCC) activity is increased during cardiac stress and would contribute to Ca^{2+} influx and expression of genes responsible for cardiac hypertrophy and heart failure (Luo et al., 2012). Several lines of evidence now show the importance of Ca_v1 channels in non-excitable cells including lymphocytes (reviewed in Robert et al., 2011, 2013). Ca_v1 channels are defined by their voltage sensitivity and their sensitivity to drugs as dihydropyridines, phenylalkylamines, benzothiazepines, known to alter T-cell functions. However the drug concentrations needed were higher compared to excitable cells. The absence of cell membrane depolarization upon activation and possible non-specific effects of the drugs questioned the putative role of Ca_v1 channels in T-cells.

Ca_v1 channels are formed by the ion forming pore α1 subunit encoded by four genes conferring some tissue-specific expression pattern in excitable cells. $Ca_v1.1$ is characteristic of skeletal muscle cells. $Ca_v1.2$ is found in neurons, heart, and smooth muscle cells while $Ca_v1.3$ is detected in neuroendocrine cells. $Ca_v1.2$ and $Ca_v1.3$ can be found in the same tissues even if their role is not redundant as shown by the differential phenotypes of $Ca_v1.2$ and $Ca_v1.3$ null mice. $Ca_v1.4$ is the retinal form. Ca_v1 channel isoforms differ by their sensitivity to depolarization and to antagonizing drugs such as dihydropyridines (DHP) as well as by their inactivation properties (Lipscombe et al., 2004). For example, $Ca_v1.4$ channels activate at more negative potentials than $Ca_v1.3$ and $Ca_v1.2$, which highlights the potential involvement of $Ca_v1.4$ in non-excitable cells as mast cells (McRory et al., 2004) and more recently in mouse T-lymphocytes (Omilusik et al., 2011).

CALCIUM IN T-LYMPHOCYTES: PROMINENT ROLE OF THE STIM-ORAI PATHWAY

In T-lymphocytes, Ca^{2+} ions are important for the activation of many enzymes including phospholipase C gamma (PLCγ), classical protein kinases C, for proper protein folding, for the accessibility of key enzymes in T-cell transduction, and as a second messenger (Vig and Kinet, 2009). Variations in the intracellular calcium concentration ($[Ca]_i$) are responsible for modulating the transcription of more than 75% of genes induced or down-regulated by T-cell receptor engagement in T-lymphocytes (Feske et al., 2001). The intracellular $[Ca]_i$ that decides the cellular fate is tightly regulated in both resting and activated conditions. The calcium concentration in the external medium is about 1–2 mM, whereas the $[Ca]_i$ is about 50–100 nM and depends on the calcium channels expressed at both the cell and endoplasmic reticulum (ER) membranes, on exchangers, pumps, … Activation of potassium channels that extrude the potassium from the cell is needed for supporting the electrochemical driving force allowing the calcium influx. In T-lymphocytes, TCR engagement results in a cascade of tyrosine kinase activation, the constitution of a platform transducing the signal with the recruitment of adapters and enzymes such as PLCγ that generates inositol trisphosphate (IP3) and diacylglycerol. IP3 binds to its receptors on the ER membrane leading to the release of ER Ca^{2+} stores, which induces a conformational change of STIM1, an ER Ca^{2+} sensor. STIM1 then localizes near the cell membrane, and activates the SOCC ORAI1 at the cell membrane (Barr et al., 2009; Oh-hora, 2009; Vig and Kinet, 2009; Zhou et al., 2010). The sustained entry of Ca^{2+} into the cell through ORAI channels is responsible for the activation of calcineurin, resulting in the nuclear translocation of the transcription factor NFAT as well as the activation of calmodulin kinase-dependent pathways. The severe immunodeficiency observed in mice or Humans with defective STIM1 (Picard et al., 2009) and ORAI1 testifies the importance of these molecules in T-cell biology (Partiseti et al., 1994; Feske et al., 2006, 2012).

However, this scheme accounts neither for the heterogeneity of calcium responses induced by TCR stimulation depending upon the state of activation and differentiation of T-lymphocytes nor for the possible implication of other calcium channels at the T-cell membrane.

Ca_v1 CHANNELS IN T-CELLS

An increasing line of evidence pleads for the involvement of Ca_v1 channels in T-lymphocyte biology (Kotturi et al., 2003, 2006; Stokes et al., 2004; Kotturi and Jefferies, 2005; Badou et al., 2006; Matza et al., 2008, 2009; Jha et al., 2009). Thus, the analysis of mice with ablation of the auxiliary subunits $Ca_vβ3$ (Jha et al., 2009) and $Ca_vβ4$ (Badou et al., 2006) and more recently of mice deleted for $Ca_v1.4$ (Omilusik et al., 2011) reveals the role of Ca_v1 channels in T-lymphocyte survival and activation. $Ca_v1.4$ was recently described as interacting with Vav and lck src kinase (Jha et al., 2009), which could result in Ca^{2+} entry required for maintaining $[Ca]_i$ and the ER Ca^{2+} stores (**Figure 1A**). As a consequence, $Ca_v1.4$ defective T-cells are more prone to apoptosis and have a reduced homeostatic proliferation capacity. Naïve $Ca_v1.4$ null T-cells also harbor defective calcium

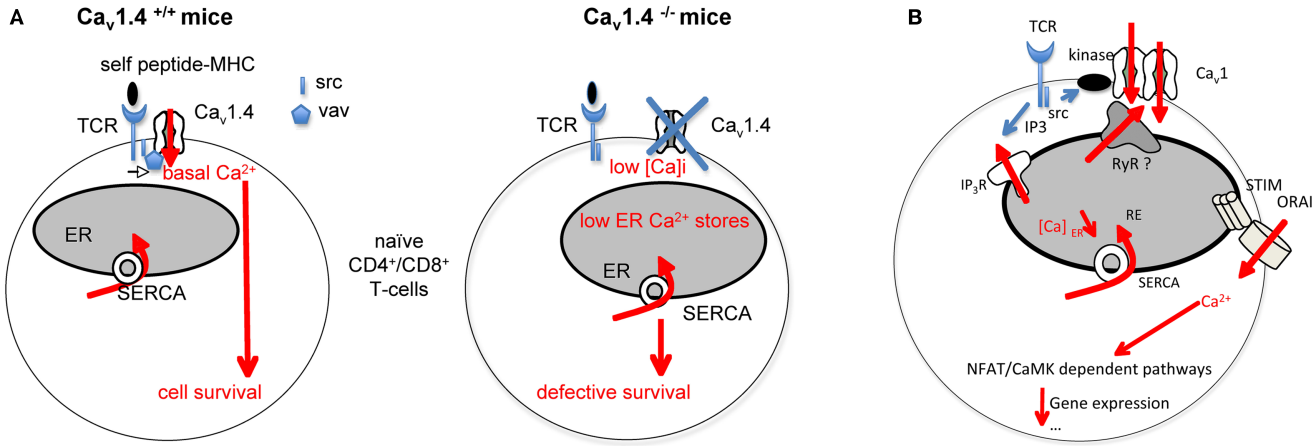

FIGURE 1 | Role of Ca$_v$1 channels in T-cell Ca^{2+} responses and functions. (A) Ca$_v$1.4 is found localized in preformed complexes containing src kinase and Vav. Self peptide-MHC interactions with the TCR, independently of the antigen specificity would induce a survival signal in naïve T-cells. This signal requires some calcium entry depending upon the Ca$_v$1.4 containing complex. Ca$_v$1.4 would be also important for maintaining correct endoplasmic reticulum (ER) Ca^{2+} stores. Ca$_v$1.4 null T-cells exhibit defective calcium homeostasis associated with defective survival. **(B)** The scheme depicts how we assume Ca$_v$1.2 channel regulation in Th2-cells. TCR activation would lead to src and PKC enzyme activation. Possible PKC-Ca$_v$1.2 interactions would induce Ca$_v$1.2 channel opening. Ca$_v$1.2 channels can interact with Ryanodine receptors (RyR) at the membrane of the endoplasmic reticulum (ER). These channels release Ca^{2+} from the ER into the cytosol. The depletion of ER Ca^{2+} stores would allow conformational changes of the Ca^{2+} sensor STIM and the subsequent activation of ORAI channels. IP3R, IP3 receptors; MHC, major histocompatibility complex; SERCA, sarco/endoplasmic reticulum Ca^{2+} ATPase; TCR, T-cell receptor.

influx upon TCR stimulation suggesting the involvement of these channels in TCR-dependent Ca^{2+} signaling (Omilusik et al., 2011). Interestingly, the human Timothy syndrome which is associated to mutation in gene encoding for Ca$_v$1.2 resulting in excessive Ca^{2+} entry is associated in most patients with an immunosuppression suggesting a role for Ca$_v$1.2 channels in immune functions (Liao and Soong, 2010). It will be interesting to determine if and how the Ca$_v$1.2 mutation affects immune cell functions.

Ca$_v$1 CHANNELS IN Th2-CELLS

Depending upon the strength of TCR stimulation, the chronicity of antigenic exposure, the route of antigen administration, and the cytokines present during T-cell differentiation, CD4$^+$ T-cells can differentiate into Th1, Th2, and Th17-cells that produce distinct sets of cytokines and exert different functions. In addition, these subpopulations express lineage specific and common transcription factors. Th1-cells produce gamma interferon (IFN-γ) and are implicated in the eradication of intracellular pathogens, viruses; Th2-cells produce interleukin (IL)-4, IL-5, and IL-13, contribute to the elimination of parasites and Th17, producing IL-17 and IL-22, participate in the elimination of extracellular pathogens as fungi. These subsets may also be pathogenic. Th1 and Th17 can promote autoimmune diseases, whereas Th2-cells can cause allergic diseases. Especially, Th2-cells can induce all the cardinal features of allergic asthma through all the cytokines they produce.

The calcium signature differs between Th1, Th2, and Th17-cells suggesting that components regulating calcium entry may differ between each T-cell subsets. The resting [Ca]i is the lowest in Th1, the highest in Th2, and intermediate in Th17. Conversely the TCR-dependent increase in [Ca]i is the highest in Th1, intermediate in Th17, and less important and sustained in Th2-cells, which could be related to the differential dependence of calcium-regulated transcription factors as NFAT, NFkB, and CREB (Dolmetsch et al., 1997) in the different T-cell subsets. It was suggested that these differences could result from lower equipment in pumps or in potassium channels required for maintaining the electrochemical driving force that supports calcium entry in Th2-cells, compared with the other T-cell subsets (Fanger et al., 2000). Our group identified voltage-dependent calcium Ca$_v$1.2 and Ca$_v$1.3 channels as selectively overexpressed in Th2-cells (Badou et al., 1997; Savignac et al., 2001, 2004; Gomes et al., 2006; Djata Cabral et al., 2010). Knocking down Ca$_v$1.2 and/or Ca$_v$1.3 α1 subunits by transfection with specific antisense oligodeoxynucleotides (Ca$_v$1AS) did not affect the proliferative response of Th2-cells but strongly impaired the TCR-dependent increase in [Ca]$_i$ and Th2 cytokine production without any effect on Th1-cells. We have then injected OVA-specific DO11.10 transgenic Th2-cells transfected or not with Ca$_v$1.2 plus Ca$_v$1.3 AS into BALB/c mice that were given intranasal OVA. Th2 Ca$_v$1AS localized into the lungs and proliferated as well as control Th2-cells. However they were unable to support a sustained inflammation characteristic of asthma. On the contrary, Th1 Ca$_v$1AS were as effective as control Th1-cells in the induction of inflammation. Antisense oligodeoxynucleotides were shown to remain localized into the airways when given by inhalation (Tanaka and Nyce, 2001). A mixture of Ca$_v$1.2 and Ca$_v$1.3 AS given by this route protected mice against the development of asthma (Djata Cabral et al., 2010), suggesting that these channels may represent an interesting new approach in the treatment of allergic diseases. Interestingly TCR stimulation is associated with polarized signaling as shown by an enrichment of Ca^{2+} (Lioudyno et al., 2008) and other ionic channels near the immune synapse, an area where the T-cell membrane contacts the antigen-presenting cell (Cahalan

and Chandy, 2009). It will be important to assess whether Ca_v1 channels traffic at the immune synapse upon TCR activation, in which areas and to identify the partners with which they associate.

Another important feature of the regulation of $[Ca]_i$ will be the understanding of ionic channels as potassium and non-specific cationic channels in Ca_v1 channel opening. Indeed K^+ channels comprising voltage and Ca^{2+}-activated channels maintain the electrochemical gradient of Ca^{2+} required for Ca^{2+} entry and tend to hyperpolarize the cell membrane favoring Ca_v1 channel inactivation. Conversely, TCR-dependent TRPM4 activation induces Na^+ entry described as limiting the Ca^{2+} entry and permitting Ca^{2+} oscillations (Launay et al., 2004). It would be interesting to determine if TRPM4 can favor Ca_v1 channel opening.

REGULATION OF Ca_V1 CHANNELS IN LYMPHOCYTES

All the authors showing the presence of Ca_v1 channels in T-lymphocytes agree that these channels are not voltage-operated in physiological conditions. Therefore, how they are regulated in T-lymphocytes must be explained. Differences in the sequence/structure of Ca_v1 channels in T-cells relative to the canonical forms in excitable cells have been reported and could provide an account for the absence of voltage sensitivity in T-cells (Stokes et al., 2004; Kotturi and Jefferies, 2005). However, the authors must demonstrate that the truncated Ca_v1 channels are true Ca^{2+} channels. The analysis of T-lymphocytes from $Ca_v1.4$ null and sufficient mice reveals the presence of voltage-gated currents in control cells, which were undetectable in null T-cells (Omilusik et al., 2011). Noticeably, the authors used peculiar conditions for their patch clamp experiments and mentioned that normal T-cells were pre-activated before recordings. This suggests that TCR activation could induce or enhance the number of Ca_v1 channels at the cell membrane. The TCR-induced opening of Ca_v1 channels may alternatively be explained by the existence of partners able to drive channel recruitment via two non-exclusive pathways: (i) post-translational modifications regulating $Ca_v1.2$ channel availability at the cell membrane without voltage change and/or (ii) modification of channel trafficking, targeting, recycling, or degradation induced by TCR stimulation. We demonstrate that the sequence of Ca_v1 channels in Th2-lymphocytes is similar to neuronal forms of the channel. However, Ca_v1 channels do not seem to be voltage-operated in Th2-lymphocytes. We have already demonstrated that TCR-induced L-type dependent calcium influx is at least sensitive to Src kinases and the PKC in an IL-4 producing T-cell hybridoma (Savignac et al., 2001). In fact, the application of PP2, an inhibitor of Src kinases or an inhibitor of PKCα on Th2-cells suppresses the Ca_v1 channel-dependent Ca^{2+} influx. In addition, we showed that PKC activator induced an entry of Ca^{2+}, suppressed by an antagonist of Ca_v1 channels (Savignac et al., 2001). These data mean that kinase activation is implicated in Ca_v1 dependent currents (**Figure 1B**). PKCα is a good candidate since $Ca_v1.2$ channels can be constitutively activated at the resting potential of smooth arteriolar cells due to their interaction with PKCα (Navedo et al., 2005; Santana and Navedo, 2010). Ryanodine receptors (RyR) are channels releasing Ca^{2+} from the ER into the cytosol. They are activated directly or not by Ca_v1 channels. It is not known if Ca_v1 channels interact with RyR in T-lymphocytes, inducing ER Ca^{2+} depletion and the activation of the STIM-ORAI pathway (**Figure 1B**).

The pending questions deal with how Ca_v1 channels work in lymphocytes and their integration with other channels to generate a specific calcium signature. The relationships between STIM, ORAI, and Ca_v1 are puzzling. STIM was shown as a negative regulator of Ca_v1 signaling (Park et al., 2010). The possibility of a checkpoint controlling ORAI versus Ca_v1 channel-dependent calcium responses merits to be explored.

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