Ca\(^{2+}\) influx in T cells: how many Ca\(^{2+}\) channels?

Stefan Feske*

Department of Pathology, New York University Langone Medical Center, New York, NY, USA
*Correspondence: feskes01@nymc.org

Edited by:
Gergely Toldi, Semmelweis University, Hungary

Reviewed by:
Gergely Toldi, Semmelweis University, Hungary

Ca\(^{2+}\) signals are critical for T cell function. A number of ion channels regulate Ca\(^{2+}\) influx from the extracellular space in T cells, either by conducting Ca\(^{2+}\) ions or by modulating the membrane potential that provides the driving force for Ca\(^{2+}\) influx (Cahalan and Chandy, 2009; Feske et al., 2012). The best characterized Ca\(^{2+}\) channel in T cells is the Ca\(^{2+}\) release-activated Ca\(^{2+}\) (CRAC) channel, which mediates store-operated Ca\(^{2+}\) entry (SOCE) in response to T cell receptor (TCR) activation and is composed of ORAI1 and open the CRAC channel pore, resulting in sustained Ca\(^{2+}\) influx. The molecular regulation of CRAC channel function has been described in detail elsewhere (Shaw et al., 2012).

The essential role of CRAC channels for T cell function and adaptive immunity is best illustrated by patients with loss-of-function or null mutations in ORAI1 or STIM1 genes, whose T cells lack CRAC channel function and SOCE (Partiseti et al., 1994; Le Deist et al., 1995; Feske et al., 1996; McCarl et al., 2009; Picard et al., 2009; Feske, 2011; Fuchs et al., 2012). CRAC channel-deficient T cells proliferate poorly in vitro and have a profound defect in the production of cytokines such as IFN\(\gamma\), TNF\(\alpha\), IL-2, and IL-17. Similar defects are found in CD4\(^+\) and CD8\(^+\) T cells from Stim1\(^{-/-}\), Orai1\(^{-/-}\), and Orai1\(^{R81W}\) knock-in mice (Gwack et al., 2008; Beyersdorf et al., 2009; McCarl et al., 2010). SOCE-deficient T cells were found to be more resistant to apoptotic cell death and showed migration defects in vitro and in vivo (Ma et al., 2010; Kim et al., 2011; Greenberg et al., 2013) (and Stefan Feske unpublished data). Interestingly, SOCE is dispensable for the development and selection of conventional TCR\(\alpha\beta\) CD4\(^+\) and CD8\(^+\) T cells in SOCE-deficient patients and mice. However, their T cell function is severely compromised in vivo, apparent in absent delayed type hypersensitivity (DTH) responses to recall antigens in patients and mice (Le Deist et al., 1995; Feske et al., 1996; McCarl et al., 2010) and impaired skin allograft rejection in Orai1\(^{R81W}\) knock-in mice (McCarl et al., 2010). Most importantly, impaired T cell function in ORAI1 and STIM1-deficient patients results in recurrent and chronic infections with a wide spectrum of viral, bacterial and fungal pathogens (Partiseti et al., 1994; Le Deist et al., 1995; Feske et al., 1996; McCarl et al., 2009; Picard et al., 2009; Byun et al., 2010; Feske, 2010; Fuchs et al., 2012).

Besides immunity to infection, CRAC channels in T cells regulate immunological tolerance and inflammation. CD4\(^+\) T cells from mice lacking ORAI1 or STIM1 function showed strongly impaired expression of proinflammatory cytokines such as IFN\(\gamma\) and IL-17 (Ma et al., 2010; McCarl et al., 2010). Importantly, these mice were resistant to T cell-mediated intestinal and CNS inflammation in animal models of colitis and multiple sclerosis. Complete absence of CRAC channel function in mice with T cell-specific deletion of Stim1 and Stim2 genes, in addition, results in impaired development and function of Foxp3\(^+\) regulatory T (Treg) cells (Oh-Hora et al., 2008). As a result, STIM1/2-deficient mice over time develop severe myelo-lymphoproliferative disease with lymphadenopathy, splenomegaly, and pulmonary inflammation (Oh-Hora et al., 2008). Intriguingly, these mice show an exocrine gland autoimmune disease resembling Sjogren’s syndrome in humans (Cheng et al., 2012). Reduced numbers of Treg cells are also found in ORAI1- and STIM1-deficient patients (Picard et al., 2009) (and unpublished data), most of which suffer from autoimmune thrombocytopenia and hemolytic anemia due to autoantibodies against erythrocytes and platelets (Feske, 2011). The complete lack of SOCE in STIM1/2-deficient mice not only impaired the development of Treg cells but also that of natural killer T (NKT) cells and TCR\(\alpha\beta\) CD8\(^{+}\) intraepithelial lymphocytes (IEL) in the gut (Oh-Hora et al., 2013). These findings indicate that low to moderate SOCE is sufficient for the postselection maturation of agonist-selected T cells (Treg...
cells, NKT cells, IEL), whereas strong SOCE is required for the proinflammatory function of Th1 and Th17 cells.

Transient receptor potential channels belong to a large family of ion channels, which conduct monovalent and divalent cations including Ca\(^{2+}\) (Nilius and Owsianik, 2011). Before the discovery of ORAI1 as the CRAC channel, several TRPC channels were proposed to mediate Ca\(^{2+}\) influx in T cells. However, a significant role of TRPC channels in Ca\(^{2+}\) influx and T cell mediated immune function has not been established.

By contrast, TRPM7 is essential for T cell development as mice with T cell-specific deletion of Trpm7 had a severe block in T cell development at the CD4\(^{+}\)CD8\(^{+}\) double negative stage (Jin et al., 2008). This is the most profound effect of any ion channel on lymphocyte development demonstrated so far. TRPM7 is Mg\(^{2+}\) permeable and widely considered to regulate cellular Mg\(^{2+}\) homeostasis. However, T cells from Trpm7\(^{-/-}\) mice had normal Mg\(^{2+}\) influx and total Mg\(^{2+}\) levels, raising the question whether impaired T cell development is caused by dysregulated Mg\(^{2+}\) homeostasis or rather by impaired influx of other cations including Ca\(^{2+}\) which TRPM7 is able to conduct as well. Another TRPC channel, TRPM2 is a non-selective, Ca\(^{2+}\) permeable cation channel that can be activated by cADPR and NAADP in human T cells (Beck et al., 2006). Increased cADPR levels after TCR stimulation (Guse et al., 1999) activate SOCE by releasing Ca\(^{2+}\) from the ER through RyR channels and potentially activate TRPM2 channels directly. TRPM7 is a non-selective cation channel implicated in Mg\(^{2+}\) homeostasis in T cells; whether its ability to conduct Ca\(^{2+}\) contributes to T cell function and how it is activated by TCR stimulation is not understood. The Ltype Ca\(_{v}\) channels Ca\(^{2+}\)2, Ca\(^{2+}\)3, and Ca\(^{2+}\)4, which mediate depolarization-dependent Ca\(^{2+}\) influx in excitable cells including neurons may contribute to Ca\(^{2+}\) influx in T cells but their activation mechanism is unknown and their current properties are not well defined. P2X receptors are non-selective Ca\(^{2+}\) channels activated by extracellular ATP. Several homologs, P2X1, P2X4, and P2X7, were reported to mediate Ca\(^{2+}\) influx in T cells in vitro.

Voltage-gated Ca\(^{2+}\) (Ca\(_{v}\) ) channels are highly Ca\(^{2+}\) selective channels that play an important role in Ca\(^{2+}\) influx and the function of electrically excitable cells such as neurons following cell depolarization (Tsien et al., 1987). In T cells, several members of the L-type family of Ca\(_{v}\) channels (Ca\(_{v}\)1) were reported to be expressed but their contribution to Ca\(^{2+}\) influx has remained controversial (Hogan et al., 2010). Recent studies showed that genetic deletion of Ca\(_{v}\)1.4 in mouse T cells and knockdown of Cav1.2 and Cav1.3 in human T cells attenuates TCR-induced Ca\(^{2+}\) influx (Cabral et al., 2010; Omlusik et al., 2011). Similarly, mutation of the regulatory β3 and β4 subunits of Ca\(_{v}\)1 channels in mice results in reduced Ca\(^{2+}\) influx and impaired IL-4, IFNγ, and TNFα production in CD4\(^{+}\) and CD8\(^{+}\) T cells following TCR stimulation (Badou et al., 2006; Jha et al., 2009). CD8\(^{+}\) T cells lacking functional β3 regulatory subunits or Cav1.4 channels were more susceptible to apoptosis (Jha et al., 2009; Omlusik et al., 2011). Cav1.4-deficient mice also showed reduced cytotoxic function of CD8\(^{+}\) T cells in vivo and impaired CD8\(^{+}\) T cell responses to infection with Listeria monocytogenes in vivo (Omlusik et al., 2011). Despite these intriguing findings, the pathways by which TCR signaling activates Ca\(_{v}\)1 channels are unknown. In contrast to excitable cells, depolarization of T cells fails to open Ca\(_{v}\)1 channels and mediate Ca\(^{2+}\) influx. It has been speculated that Ca\(_{v}\)1 channels in T cells are activated by an alternative,
Intriguingly, these currents were abolished
ological properties of CaV1 channels in T
ies will need to investigate the electrophysi-
mation were observed in
X
P2
decreased (Sharp et al., 2008) CNS inflam-
immunity, however, is ambiguous as both
The role of P2X7 in T cell-mediated auto-
function of Th17 cells and inhibiting the
or chemical antagonists attenuated Ca
of P2X1, P2X4, and P2X7 function by RNAi
et al., 1996) and IL-2 production (Adinolfi
Activation of enzymes such as calcineurin,
the contributions of TRP, Ca1, and P2X
receptor channels remain to be more clearly
defined. These channels could contribute to
Ca2+ influx in specific T cell subsets, at
distinct stages of T cell development or fol-
lowing stimuli other than TCR engagement.
A better understanding of the contributions of
different Ca2+ influx pathways in T cells will
be essential to define potential drug tar-
targets for the modulation of T cell function in
a variety of diseases caused by aberrant
T cell function.

ACKNOWLEDGMENT
This work was funded by NIH grant
A1097302.

REFERENCES
Adinolfi, E., Callegari, M. G., Ferrari, D., Bolognesi, C.,
Minelli, M., Wierckowski, R. M., et al. (2005). Basal
activation of the P2x7 ATP receptor elevates
mitochon-drial calcium and potential, increases cellular
ATP levels, and promotes serum-independent growth.
Mol. Biol. Cell 16, 3260–3272.
Adriouch, S., Doss, C., Welge, V., Seman, M., Koch-Nothe,
F., and Haug, F. (2002). Cutting edge: a natural P451L
mutation in the cytoplasmic domain impairs the
function of the mouse P2X7 receptor. J. Immunol.
169, 4108–4112.
Badoz, A., Jha, M. K., Matza, D., Mehal, W. Z., Freichel,
M., Flockerzi, V., et al. (2006). Critical role for
the beta regulatory subunits of Cav channels in T lymph-
ocyte function. Proc. Natl. Acad. Sci. U.S.A. 103,
15529–15534.
Baricordi, O. R., Ferrari, D., Melchiorri, L., Chiozzi, P.,
Hanau, S., Chiari, E., et al. (1996). An ATP-activated
purinoreceptor during differentiation of the exocrine
gland autoimmune disease, Sjogren’s syndrome. Proc.
Natl. Acad. Sci. U.S.A. 109, 14544–14549.
Chesn, T. M., Apasov, S., and Sitkovsky, M. (1996).
Murine T lymphocytes modulate activity of an ATP-
activated P2x7-type purinoreceptor during differentia-
tion. J. Immunol. 157, 1371–1380.
Di A., Gao, X. P., Qian, F., Kawamura, T., Han, J., Hecquet,
C., et al. (2011). The redox-sensitive cation channel
TRPM2 modulates phagocyte ROS production and
inflammation. Nat. Immunol. 13, 29–36.
Feri, D., Piriziani, C., Adinolfi, E., Lemoli, R. M., Curti,
A., Ildiko, M., et al. (2006). The P2x7 receptor: a key
player in IL-1 processing and release. J. Immunol.
176, 3877–3883.
Feske, S. (2007). Calcium signalling in lymphocyte acti-
vation and disease. Nat. Rev. Immunol. 7, 690–702.
Feske, S. (2010). CRAC channelopathies. Pflugers Arch.
460, 417–435.
Feske, S. (2011). Immunodeficiency due to defects in
stored-operated calcium entry. Annu. N. Y. Acad. Sci.
1238, 74–90.
Feske, S., Gwack, Y., Prakriya, M., Srikanth, S., Puppel,
S. H., Tanasa, B., et al. (2006). A mutation in Orai1
function. Nature 441, 179–185.
Feske, S., Muller, J. M., Graf, D., Krozek, R. A., Drager, R.,
Niemeyer, C., et al. (1996). Severe combined immu-
nodeficiency due to defective binding of the nuclear
factor of activated T cells in T lymphocytes of two
male siblings. Eur. J. Immunol. 26, 2119–2126.
Feske, S., Skolnik, E. Y., and Prakriya, M. (2012). Ion can-
nels and transporters in lymphocyte function and
immunity. Nat. Rev. Immunol. 12, 532–547.
Fuchs, S., Rensing-Ehl, A., Speckmann, C., Bengsch, B.,
Schmitt-Graeff, A., Bondzio, I., et al. (2012). Antiviral
and regulatory T cell immunity in a patient with strom-
al interaction molecule 1 deficiency. J. Immunol.
188, 1523–1533.
Greenberg, M. L., Yu, Y., Leverrier, S., Zhang, S. L.,
Parker, I., and Cahalan, M. D. (2013). Orail function
is essential for T cell homing to lymph nodes. J.
Immunol. 190, 3197–3206.
Guse, A. H., Da Silva, C. P., Berg, I., Skapenko, A. L., Weber,
K., Heyer, P., et al. (1999). Regulation of calcium sig-
alling in T lymphocytes by the second messenger
cyclic ADP-ribose. Nature 398, 70–73.
McCarl, C. A., Khalil, S., Ma, J., Oh-Hora, M., Yamashita, A., Maruyama, Y., Ogura, T., Mio, K., Kato, K., Kaneko, H., Ma, J., McCarl, C. A., Khalil, S., Luthy, K., and Feske, S. (2013). NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production. Nat. Rev. Immunol. 10, 210–215.

Tien, R. W., Hess, P., McLeskey, E. W., and Rosenberg, R. L. (1987). Calcium channels: mechanisms of selectivity, permeation, and block. Annu. Rev. Biophys. Biophys. Chem. 16, 265–290.

Vig, M., Beck, A., Billingsley, J. M., Lis, A., Parvez, S., Peineit, C., et al. (2006a). CRACM1 multimers form the ion-selective pore of the CRAC channel. Curr. Biol. 16, 2073–2079.

Vig, M., Peineit, C., Beck, A., Koomoa, D. L., Rahab, D., Koblan-Huberson, M., et al. (2006b). CRACM1 is a plasma membrane protein essential for store-operated Ca2+ entry. Science 312, 1220–1223.

Wohrle, T., Yip, L., Elklah, A., Sumi, Y., Chen, Y., Yao, Y., et al. (2010). Pannexin-1 hemichannel-mediated ATP release together with P2X1 and P2X4 receptors regulate T-cell activation at the immune synapse. Blood 116, 3475–3484.

Yamamoto, K., Sako, S., Yamamoto, T., Yoshikawa, M., Shibata, M., Ohura, N., et al. (2006). Impaired flow-dependent control of vascular tone and remodeling in P2Y4-deficient mice. Nat. Med. 12, 133–137.

Yamamoto, S., Shimizu, S., Kiyonaka, S., Takahashi, N., Wajima, T., Hara, Y., et al. (2008). TRPM2-mediated Ca2+ influx induces chemokine production in monocytes that aggravates inflammatory neutrophil infiltration. Nat. Med. 14, 738–747.

Yeromin, A. V., Zhang, S. L., Jiang, W., Yu, Y., Safrina, O., and Cahalan, M. D. (2006). Molecular identification of the CRAC channel by altered ion selectivity in a mutant of Orai. Nature 443, 226–229.

Yip, L., Wohrle, T., Corriden, R., Hirsh, M., Chen, Y., Inoue, Y., et al. (2009). Autocrine regulation of T-cell activation by ATP release and P2X7 receptors. FASEB J. 23, 1683–1693.

Zhang, S. L., Yeromin, A. V., Zhang, X. H., Yu, Y., Safrina, O., Penna, A., et al. (2006). Genome-wide RNAi screen of the ion-selective pore of the CRAC channel. Curr. Biol. 16, 2073–2079.

Tschopp, J., and Schroder, K. (2010). NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production. Nat. Rev. Immunol. 10, 210–215.

Received: 18 March 2013; accepted: 12 April 2013; published online: 24 April 2013.

Citation: Feske S (2013) Ca2+ influx in T cells: how many Ca2+ channels? Front. Immunol. 4:99. doi:10.3389/fimmu.2013.00099

This article was submitted to Frontiers in T Cell Biology, a specialty of Frontiers in Immunology.

Copyright © 2013 Feske. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in other forums, provided the original authors and source are credited and subject to any copyright notices concerning any third-party graphics etc.