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Review

ORAI-mediated calcium influx in T cell proliferation, apoptosis and tolerance

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ABSTRACT

Ca^{2+} homeostasis controls a diversity of cellular processes including proliferation and apoptosis. A very important aspect of Ca^{2+} signaling is how different Ca^{2+} signals are translated into specific cell functions. In T cells, Ca^{2+} signals are induced following the recognition of antigen by the T cell receptor and depend mainly on Ca^{2+} influx through store-operated CRAC channels, which are mediated by ORAI proteins following their activation by STIM proteins. The complete absence of Ca^{2+} influx caused by mutations in *Stim1* and *Orai1* leads to severe immunodeficiency. Here we summarize how Ca^{2+} signals are tuned to regulate important T cell functions as proliferation, apoptosis and tolerance, the latter one being a special state of immune cells in which they can no longer respond properly to an otherwise activating stimulus. Perturbations of Ca^{2+} signaling may be linked to immune suppressive diseases and autoimmune diseases.

1. Introduction

Naïve T cells reside in lymph nodes ready to encounter their corresponding antigen-presenting cells (APC), which are mostly dendritic cells in lymph nodes. After recognizing its specific antigen–major histocompatibility complex (MHC) on APC, a naïve T cell will be activated, and will subsequently differentiate and proliferate to generate a clonal population of antigen-specific effector T cells. This population of armed effector T cells is required to efficiently eliminate the identified antigen. The close contact zone between a T cell and the APC is called the immunological synapse (IS) where reorganization and activation of receptors, which are involved in recognition and adhesion, initiate different signaling cascades including Ca^{2+} signaling [1]. The activation of T cell receptors (TCR) through MHC-antigen complexes induces the activation of store-operated Ca^{2+} (SOC) channels and subsequent $[Ca^{2+}]_i$ elevations required for T cell activation.

Immune cells have been instrumental to define SOC channels and to identify their molecular identity. Following the concept of Putney, who defined SOC entry, or as it was called back then, capacitative Ca^{2+} entry [2], it took six years to record the first SOC current named I_{crac} in mast cells [3] and in T cells [4]. It was not until 2006 that ORAI proteins were identified as the main molecular players to form CRAC channels [5–7]. A year before in 2005, very good evidence had already been presented that CRAC channels were activated by STIM proteins [8,9] which reside in the membrane of the calcium stores within the endoplasmic reticulum and sense the store filling with their intra-luminal EF-hand. Two STIM proteins and three ORAI channels have been found in humans and mice and different STIM/ORAI combinations can form CRAC channels when expressed heterologously [10]. The major combination to form CRAC channels appears to be STIM1/ORAI1, and loss of function mutations of either one of these in humans causes massive defects in T cell based immunity [11] with bone marrow transplantation currently being the only available treatment for this immune deficiency.

Abbreviations: AICD, activation induced cell death; AIRE, autoimmune regulator; APC, antigen-presenting cell; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration; CRAC channel, Ca^{2+} release-activated Ca^{2+} channel; CREB, cyclic-AMP-responsive element-binding protein; GALT, gut-associated lymphoid tissue; DISC, death-inducing signaling complex; IBD, inflammatory bowel disease; IP_3R, IP_3 receptor; LPL, lamina propria lymphocytes; MEF2, myocyte enhancer factor 2A; MHC, major histocompatibility complex; NFAT, nuclear factor of activated T cells; SOC, store-operated Ca^{2+}; TCR, T cell receptors; Treg, regulatory T cell.

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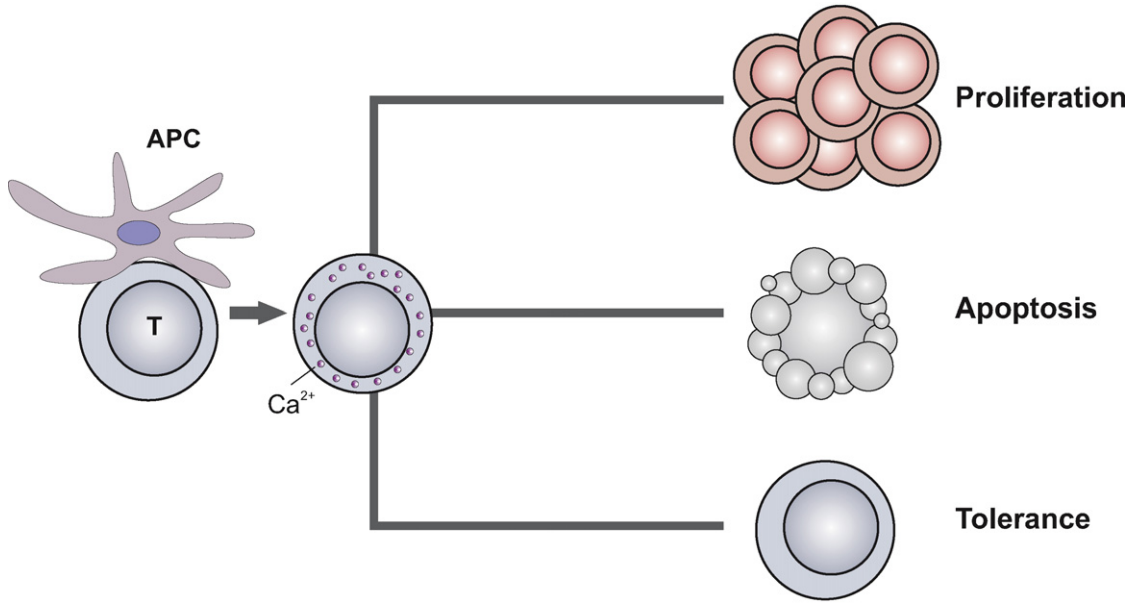

Fig. 1. T cell fate: proliferation, apoptosis and tolerance. Ca^{2+} signals are required for T cell activation following IS formation with APC through the recognition of antigen by the TCR. The magnitude and shape of Ca^{2+} signals control the transcriptional activity of T cells and therefore modulate proliferation, apoptosis and tolerance of T cells.

While CRAC channels and ORAI1 proteins have been reported in many different tissues, they are best studied in cells of the immune system where I_{crac} can be relatively easily recorded despite its small size. In other tissues, Ca^{2+} imaging rather than patch clamp measurements have been the major tool to characterize SOC entry: SOC entry is often mediated by CRAC channels but there is considerable evidence for other SOC channels as well [12,13]. Cell activation and proliferation often depend on SOC entry, and also cell survival and apoptosis appear to depend on the activity of these Ca^{2+} channels [14].

In T cells, CRAC channels are thus by far the major functionally important Ca^{2+} entry pathway and it is not surprising that CRAC and ORAI1 are absolutely required for T cell functions. Differential Ca^{2+} signals can be translated into specific transcription factor profiles which are then linked to T cell proliferation, apoptosis or tolerance [15]. Among these transcription factors, the nuclear factor of activated T cells (NFAT) family has an outstanding role. Without the concomitant activation of AP-1, NFAT likely induces tolerance while in combination with AP-1 and other transcription factors T cell activation and proliferation are highly favored. A rise in $[Ca^{2+}]_i$ is absolutely required for the activation of NFATs, putting Ca^{2+} in the spotlight to determine the T cell fate: activation and proliferation or apoptosis and tolerance (Fig. 1). In this review we will dissect how changes in $[Ca^{2+}]_i$ can be used by T cells to control a well-balanced immune response.

2. ORAI and STIM in T cell activation

ORAI1 and STIM1 proteins have been identified as the key players in SOC entry in T cells [5–9]. In humans and in mice three homologues of the ORAI family, ORAI1, 2 and 3, and two STIM homologues STIM1 and STIM2 have been identified. The STIM1/ORAI1 combination appears to be indispensable for SOC entry in T cells and T cell based immunity following TCR stimulation and costimulation through other receptors (Fig. 2), however the exact function of different STIM/ORAI combinations is still a subject of intensive research. Since the lack of costimulation is a major aspect for the induction of T cell tolerance, we will discuss Fig. 2 in detail in the section on the Ca^{2+}-dependent T cell tolerance.

To get further insight into STIM and ORAI functions, *Stim1* and *Orai1* were knocked-out in mice but due to their prenatal death, it was necessary to generate conditional T cell specific deletions of *Stim1* and/or *Stim2* [16,17]. The prominent role of STIM1 in SOC entry was demonstrated in primary T cells from surviving mice lacking STIM1 in which SOC entry was completely eliminated [16]. Furthermore, $CD4^+$ T cells show hyperactivity as well as hyperproliferation suggesting a role for (the absence of) Ca^{2+} signaling in lymphoproliferative diseases. Impairment of T cell function has often been associated with lymphoproliferation, which appears to counter regulate the failing of immune cells. A prominent example is the LAT (linker for activation of T cells) mutant that inhibits T cell activation but induces lymphoproliferation [18]. Lymphoproliferation may thus not be specific for STIM/ORAI mutations but rather a general phenotype induced by severe signaling deficits. It can cause massive disorders because it may lead to the accumulation of aberrant T cells and to the unopposed activation of other immune cells and autoimmune reactions with insufficient apoptosis [19].

Interestingly, T cell maturation and differentiation into effector cells was not affected by the STIM1-deficiency suggesting that thymic T cell differentiation does not necessarily require SOC influx [16]. Likewise, STIM1 and STIM2 deficient T cells developed a lymphoproliferative phenotype, but in contrast to the *Stim1* single knock-out also the number of regulatory T cells (Tregs) was clearly decreased [17]. One could argue that the loss of Tregs might be related to the lymphoproliferative disease but on the other hand, in $Stim1^{-/-}$ mice, a lymphoproliferative disease was developed but the number of Tregs was comparable to the wildtype. Treg function was, however, not tested under these conditions. Since T cell function depends on Ca^{2+} influx, it can be assumed that Ca^{2+} influx is also required for Treg function. Tregs from $Stim1^{-/-}$ mice may thus not be functional and could be involved in the lymphoproliferative phenotype.

In conditionally STIM1-deficient mice, naïve $CD4^+$ T cells did not produce IL-2 in contrast to STIM2-deficient naïve $CD4^+$ T cells whose IL-2 secretion is almost comparable to wild type [17]. Thus, STIM2 may not be able to serve as a back-up for STIM1 arguing against redundancy of the two STIMs. In contrast to naïve cells, differentiated STIM2-deficient T helper cells showed less production of IL-2, IL-4 and IFN-γ.