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Review Article

microRNA Functions Intracellular Calcium Homeostasis in Naïve CD8$^+$ T Cells

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Abstract

Functional capability of effector CD8$^+$ T cells on pathogen-infected cells to kill them requires the activation of naive CD8$^+$ T cells by triggering the stimulation of T cell receptors (TCR) and co-stimulatory molecules. The proper activation of effector CD8$^+$ T cells depends on the co-stimulation of both TCR and co-stimulatory molecules. Without co-stimulation effector CD8$^+$ T cells are unable to produce activation-inducing genes such as IL-2 and proliferate upon with specific antigen. This condition refers as the anergy formation of effector CD8$^+$ T cells. Activation and anergy formation of effector CD8$^+$ T cells depend on the intracellular Ca2$^+$ signaling, as it regulates the responsiveness of CD8$^+$ T cells. This contribution of Ca2$^+$ signaling has been well studied in effector CD8$^+$ T cells with possible molecular mechanisms. But, the specific molecular mechanisms of Ca2$^+$ signaling in naive CD8$^+$ T cells related to anergy formation have not yet been well discussed, other than our previous study which reported about the contribution of miR-150 to regulate Ca2$^+$ signaling in naive CD8$^+$ T cells thereby regulating the responsiveness. Therefore, in this review we have summarized the already known role of Ca2$^+$ signaling in naive and CD8$^+$ T cells. Specially, we have highlighted the role of miR-150 in the regulation of naive CD8$^+$ T cells' responsiveness.

ABBREVIATIONS

CRAC: Calcium Release-Activated Ca2$^+$ Channel; PMCA: Plasma Membrane Ca2$^+$ ATPase; TCR: T Cell Receptor; STIM1: Stromal-Interacting Molecule 1; TMEM20: Transmembrane Protein 20; NFAT: Nuclear factor of activated T-cells; AP-1: Activator Protein 1; ORAI1: CRAC Channel Protein 1

INTRODUCTION

Unresponsiveness of the immune system to various tissues or substances which have the ability to elicit an immune response can be termed as the immune tolerance [1]. Depending on the state where it origin, immune tolerance can be classified into central tolerance and peripheral tolerance [2,3]. Central tolerance prefers the educating immune system to discriminate self and non-self and originates in thymus and bone marrow. Whereas the peripheral tolerance, which functions to prevent the over reactivity in immune system, originates in lymph nodes or other tissues [2]. Generally, the direct induction of this peripheral lymphocyte tolerance may cause the lack of response to foreign organisms via mal-functioned defense mechanisms, which is termed as anergy [4,5]. In the state of anergy, the immune system is unable to elicit immune responses against a specific antigen. Therefore, the phenotype of lymphocytes which fail to respond to specific antigens is called as the Anergic phenotype [6,7].

Anergy induction and its underlying molecular mechanisms have been well studied in effector T cells as a type of lymphocyte which plays a major role in immune response [5,7,8]. Among T cells, the cytotoxic T cells (CD8$^+$ T cells) kill the infected or damaged cells [9]. It is essential to stimulate T cell receptors (TCR) together with its co-stimulatory molecules to trigger a balanced CD8$^+$ T cell activation [6,10]. Mainly, both CD8$^+$ T cell activation and anergy formation depend on the Calcium (Ca2$^+$) - mediated signaling pathway. Ca2$^+$ signaling pathway uses Ca2$^+$ ions to drive various cellular processes mainly as signal transduction [11]. Even though, Ca2$^+$-mediated signaling in effector CD8$^+$T cell has been studied well, the molecular mechanism in naive T cells has not yet been studied much in the literature. Naive CD8$^+$ T cells are CD8$^+$ T cells which are not yet encountered its cognate antigen [12]. But, we have showed how Ca2$^+$ signaling functions on naive CD8$^+$ T cells, especially in the mean of activation and anergy formation in one of our previous studies. According to that paper, Ca2$^+$ signaling in naive CD8$^+$ T cells can be regulated by highly expressed microRNA (miR-150), small non-coding RNA which is having 22 nucleotides [13]. MicroRNAs are small

endogenous RNAs, which is having 19-25 nucleotides [14]. Some of other previous studies also have showed that microRNAs regulate the immune tolerance or anergy in T cells including $CD8^+$ T cells [15-17].

Considering the above mentioned findings related to immune tolerance and anergy formation, especially in CD8+ T cells, we have concluded the $Ca2^+$-mediated regulation in the responsiveness of effector $CD8^+$ T cells. We also highlighted those regulations in naive $CD8^+$ T cells. Finally, we have summarized the contribution of miR150 in the activation of naive $CD8^+$ T cells and the regulation of $CD8^+$ T cell responsiveness to prevent hypo or unresponsiveness.

$Ca2^+$ mediated signaling regulates responsiveness of $CD8^+$ T cells

$Ca2^+$- mediated activation of Effector $CD8^+$ T cell: Naive $CD8^+$ T cells go through activation process after it encounters an appropriate antigen while migrating through secondary lymphoid organs. These activated Effector $CD8^+$ T cells are functionally capable to mediate effector immune responses [18,19]. Those appropriate antigens with major histocompatibility complex stimulate TCR in this activation process of effector $CD8^+$ T cells. For a proper activation, effector $CD8^+$ T cells also require parallel stimulation of co-stimulatory receptors such as CD28 [13]. Mechanistically, stimulation of TCR increases the intracellular concentration of $Ca2^+$. This results the induced nuclear translocalization of Nuclear factor of activated T-cells (NFAT), a family of transcription factors which is important in immune response (20). Parallel, the co-stimulation of CD28 activates Activator protein 1 (AP-1) through the activation of PI3K signaling pathway. Interactions of NFAT with AP-1 in a transcriptional complex can increase the expression of CD8+ T cell activation related genes. Therefore, the co-stimulation of both NFAT and AP-1 is essential for the proper activation of effector CD 8^+ T cells to be functionally capable [20,21].

Moreover, calcium release-activated $Ca2^+$ (CRAC) channel and plasma membrane $Ca2^+$ ATPase (PMCA) are important in the regulation of intracellular $Ca2^+$ concentration during $CD8^+$ T cell activation [22]. Upon TCR stimulation, the $Ca2^+$ release from Endoplasm Reticulum (ER) with the help of inositol triphosphate receptor is induced. It results the elevated level of intracellular $Ca2^+$ in cytoplasm. The higher concentration of intracellular $Ca2^+$ associates with calmodulin, a multifunctional intermediate calcium-binding messenger protein, to activate PMCA there by exporting the $Ca2^+$ from cell. On the other hand, Stromal-interacting molecule 1 (STIM1) regulates the balance of intracellular $Ca2^+$ concentration in a cell by controlling the influx of $Ca2^+$ [23]. For this function, STIM1 forms a complex with transmembrane protein 20 (TMEM20) which enable STIM1 binding to PMCA [24]. STIM1 can interact with CRAC channel protein 1 (ORAI1) there by opening CRAC channels to allow $Ca2^+$ influx into cells [23]. Furthermore, it inhibits PMCA-mediated $Ca2^+$ extrusion from cells [25]. Therefore, the complex of STIM1 and TMEM20 is contributed to keep the balance of $Ca2^+$ concentration and activation of effector $CD8^+$ T cell state. Therefore, CRAC, PMCA, STIM1 and TMEM20 play their essential roles in effector $CD8^+$ T cell activation to make them functionally capable, without inducing anergeric phenotypes. Specially, TMEM20 plays an important role in effector CD8+ T cell activation by controlling STIM1 [13].

Even though, the specific role of TMEM20 has been studied well in effector $CD8^+$ T cell during its activation, it has been not focused that much on naive $CD8^+$ T cells.

Anergy formation in effector $CD8^+$ T cell: Anergy, the unresponsiveness of immune cells considers as an important mechanism in the maintaining of peripheral immune tolerance [5]. T cell anergy inactivates the lymphocytes functionally following the appropriate antigen encounter. But, those cells with anergic phenotype remain alive for a long period under hypo responsiveness state as they are having a different life span from normal T cells [26]. Both $CD4^+$ and effector $CD8^+$ T cell anergy can be divided into two broad categories as clonal anergy and adaptive or in vivo anergy. Among them, clonal anergy is responsible for the growth arrest state while adaptive anergy tolerance is representing the inhibition of effector and proliferative functions of T cells [27].

Clonal anergy in $CD4^+$ T cells can be induced by the stimulation of strong T cell receptor (TCR) signal when the co stimulation is absent [28]. According to previous studies, conditions which can induce new protein synthesis but is not complete enough to activate of CD 4^+ T cells initiate and maintain the anergic state in $CD4^+$ T cells [27]. Similarly to $CD4^+$ T cells, effector $CD8^+$ T cells also appeared to be anti-proliferative when it is in the state of clonal anergy [29]. Other than that, Mescher and colleagues have described another form of clonal anergy in effector $CD8^+$ T cells named activation-induced non-responsiveness (AINR) [29]. Therefore, the proper co-stimulation is required to induce the activation over anergy formation in effector $CD8^+$ T cells, which were stimulated by TCR, cannot produce Interleukin 2 (IL-2) if the co-simulation of molecules such as CD28 is absent. Also, they cannot proliferate upon subsequent stimulation by antigens. In this case, NFAT homodimerizes complexes itself and induces anergy in effector $CD8^+$ T lymphocytes instead of working as a transcriptional factor [20,21,30].

Generally, the appropriate antigen should be present to T lymphocyte by an antigen presenting cell (APC) to begin productive response of effector $CD8^+$ T lymphocytes. These APC present the antigen on its MHC II complex which activates costimulatory receptors in $CD8^+$ T cell. However, when T cells interact with an antigen not presented by the APCs which is not specific, the effector $CD8^+$T cell undergoes anergy. It has also been shown that, even though, those antigens presented by APCs properly, induce the effector $CD8^+$ T cell activation only weakly. This weak stimuli still activates NFAT sufficiently, but AP-1 is not, thereby the anergistic response takes place even with the co-stimulation [21]. Strong stimulation of T-cells either by IL-2 or by TCR/costimulatory receptors can break the anergy formation [10,31].

Therefore, the $Ca2^+$ signaling in effector $CD8^+$ T cells has critical role in the T cell activation and anergy formation (Figure 1). Although controlling intracellular $Ca2^+$ levels in naïve $CD8^+$ T cells is also critical for T cell activation, regulatory molecules and associated mechanisms that determine the $Ca2^+$ signaling in naïve $CD8^+$ T cell activation and anergy formation are largely unknown.

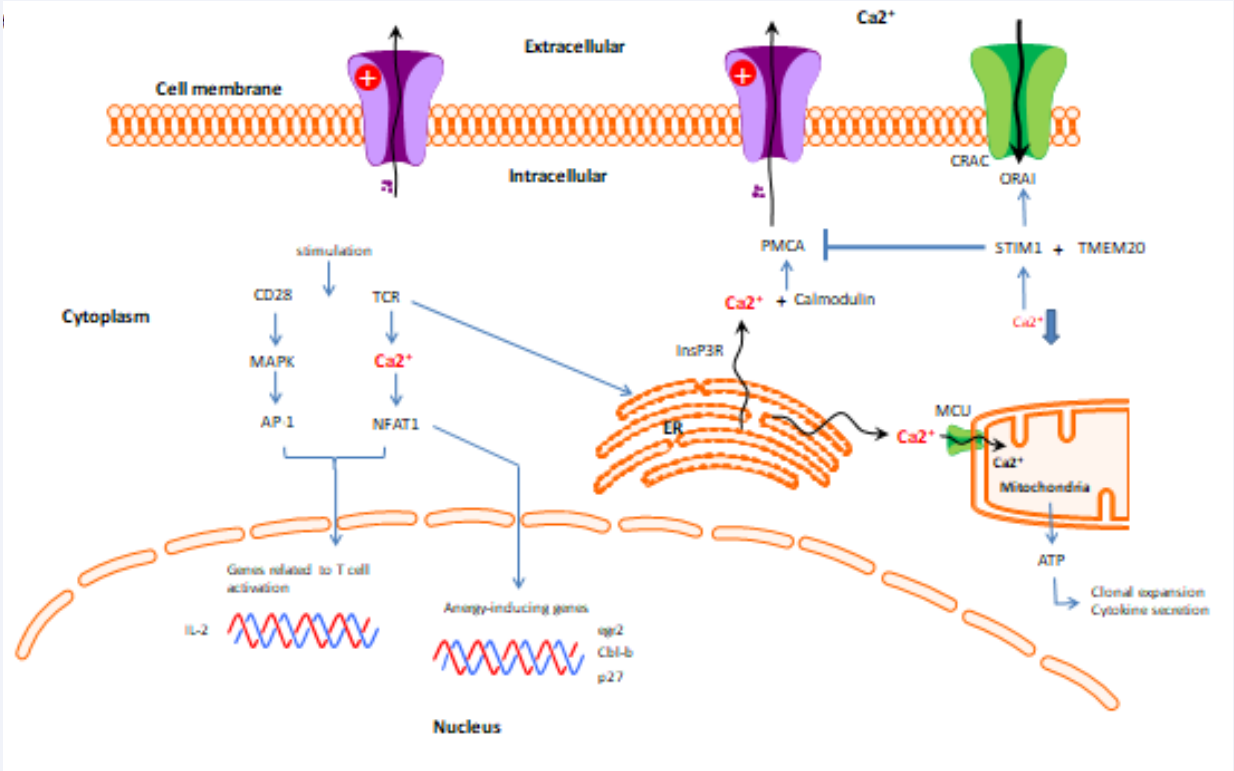

Figure 1 Ca^{2+} signaling mediates the activation and anergy formation of effector $CD8^+$ T cells

Co-stimulation of TCR and CD28 molecules results the induced expression of T cell activation-related genes via complex formation of NFAT1 activated by Ca^{2+} signaling and AP-1 activated by MAPK. Oppositely, alone stimulation of NFAT1 causes the induction of anergy-related gene expression. Further, TCR stimulation causes Ca^{2+} release from ER via activating InsP3R by increasing the intracellular Ca^{2+} concentration. Elevated level of intracellular Ca^{2+} in association with Calmodulin induces PMCA to extrude Ca^{2+} from the cell. Ca^{2+} released by InsP3R is transferred into mitochondria through the mitochondrial Ca^{2+} uniporter (MCU) which effectively couple TCR ligation to enhance ATP production required for clonal expansion and secretion of cytokines. When the concentration of Ca^{2+} reduces, the CRAC channels open to influx Ca^{2+} by the interaction of STIM1 with ORAI1, as STIM1 is capable to recognize low intracellular Ca^{2+}. Usually, the Ca2+ regulating activities of STIM1 mediate by a complex formation with TMEM20.

Contribution of miR-150 in naive $CD8^+$T cell to immune activation and tolerance via TMEM20-mediated Ca^{2+} signaling

Naive $CD8^+$ T cells migrating within secondary lymphoid organs such as spleen and lymph nodes, can get activated upon stimulation by appropriate antigen [9]. Mostly, these cognate antigens are presented by dendritic cells. Upon activation, antigen-specific $CD8^+$ T cells undergo clonal expansion and become effector $CD8^+$ T cells [32,33]. Even though, it is not yet understood well, Ca^{2+} signaling plays a pivotal role in this activation of naïve $CD8^+$ T cells and the responsiveness [13]. As a possible molecular mechanism of regulating Ca^{2+} signaling in naïve $CD8^+$ T cells, we have reported a mechanism mediated by miR-150 in our previous study [13]. Generally the level of miR-150 is higher in naïve $CD8^+$ T cells and reduces with TCR stimulation [34]. According to the above mentioned study, we showed how miR-150 controls the level of intracellular Ca^{2+} level in naïve $CD8^+$ T cells through downregulating TMEM20. MiR-150, microRNA with 22 nucleotides, acts as an essential regulator in the activation of naïve $CD8^+$ T cells by preventing hypo responsiveness and the expression of anergy-inducing genes upon TCR stimulation [13].

That study has shown that, the deficiency of miR-150 can induce the expression of anergy-inducing genes in naïve $CD8^+$ T cells by using miR-150 $^{-/-}$ naïve $CD8^+$ T cells. Mechanistically, the reduction of miR-150 in naïve CD8+ T cells induces TMEM20 expression [13]. Usually TMEM 20 co-localizes with STIM1 by making a complex to function in $CD8^+$ T cells [24]. But, in naïve T cells, TMEM20 not localizes with STIM1 and act in STIM1-independent manner. Therefore, as this study suggest, various un-identified factors which can support TMEM20 function may induce TMEM20 in miR-150 reduce conditions. Elevated TMEM20 then inactivate PMCA activities, extrusion of intracellular Ca^{2+} from cells, in naïve $CD8^+$ T cells [13]. Therefore, miR-150 induces the translocation of TMEM20 into PMCA by inactivating its functions.

However, there are many other intracellular Ca2+ regulators in $CD8^+$ T cells including Calcium release-activated channels (CRAC), sarco/endoplasmic reticulum Ca2+-ATPase (SERCA), sodium-calcium exchanger (NCX) and mitochondrial calcium uniporter (MCU) [35,36]. But in our previous study, we have proved that these regulators are not functioning in naïve $CD8^+$ T cells as similar as in $CD8^+$ effector T cells. Among those regulators, CRAC can reduce the uptake of Ca^{2+} but not the

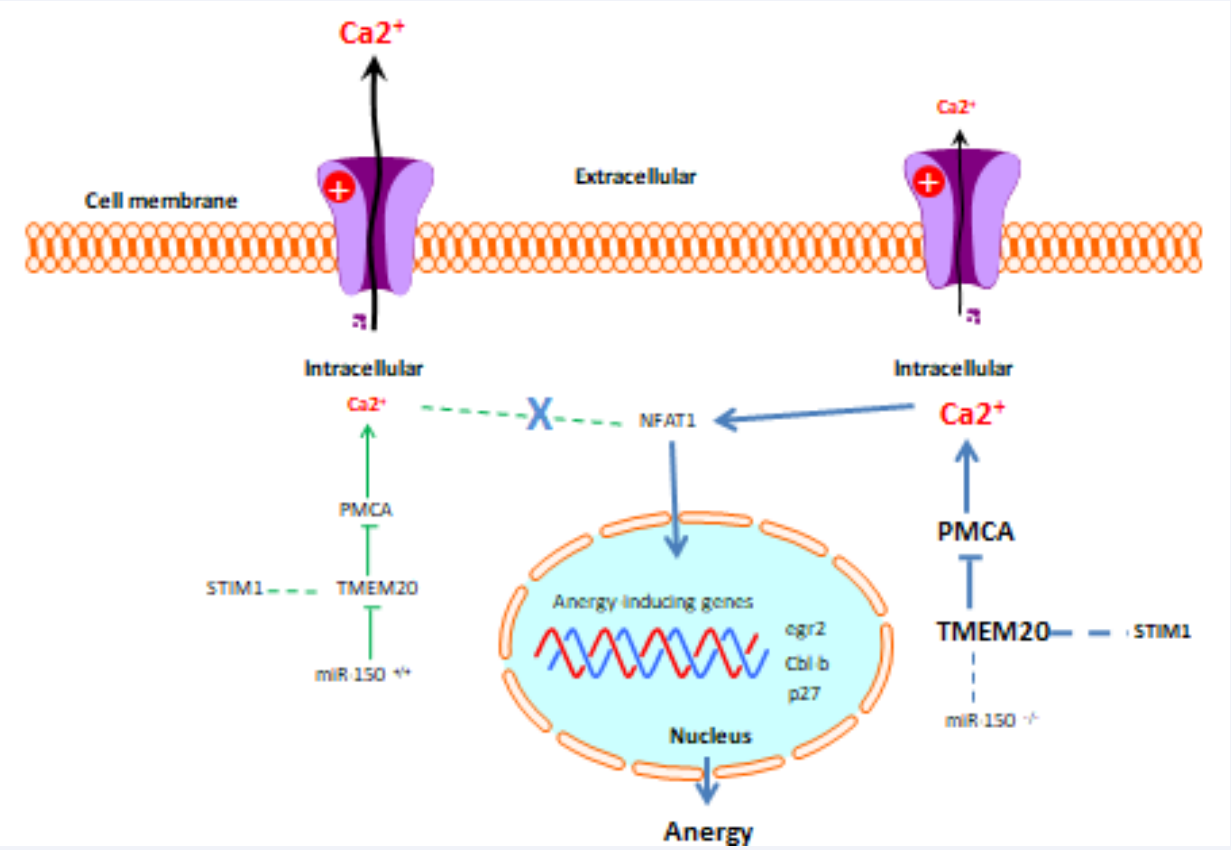

Figure 2 MiR-150 regulates the anergy formation in naive CD8+ T cells

Higher level of miR-150 in naive CD8+ T cells causes the inhibition of TMEM20 thereby inducing the activities of PMCA as an extruder of intracellular Ca2+ from cell. This extrusion helps to prevent the accumulation of intracellular Ca2+ in a cell thereby preventing the induction of anergy-inducing genes expression and anergy formation in naive CD8+ T cells. On the other hand, If the miR150 knockdown in naive CD8+ T cells, it results the accumulation of intracellular Ca2+ through induced TMEM20, thereby inducing the anergy formation.

overall intracellular Ca2+ level. Therefore, the overall role of CRAC is limited in naïve CD8+ T cells compared to CD8+ effector T cells. Similarly, SERCA and NCX also are in inactivated conditions because those regulators are activated upon TCR stimulation [13]. When consider MCU, functions associate with mitochondria relocation [37]. Therefore, it is inactivated in naïve CD8+ T cells as it has un-polarized mitochondria at Ca2+ influx site. Thus, the function of MCU as Ca2+ regulator is different from CD8+ T cells which mitochondria relocate in immunological synapse.

Induced intracellular Ca2+ level in naïve CD8+ T cells by induced TMEM20 in miR-150 reduced conditions causes the elevation of NFAT activities thereby increase the expression of anergy-inducing genes such as Egr2, cbl-b and p27. Therefore, the reduction of miR-150 in naïve CD8+ T cells results induced expression of anergy-inducing genes (Figure 2) [13].

DISCUSSION & CONCLUSIONS

The responsiveness, activation and anergy formation, of effector and naive CD8+ T cells is regulated by the ca2+ signaling. Both cells have differences in the underlying molecular mechanisms of this regulation. To date, the mechanisms in effector CD8+ T cells have been well-studied. But, it is remaining to study more in naive CD8+ T cells. According to a paper published by our group previously, in miR-150 reduced conditions of naïve CD8+ T cells induce the anergy formation by inducing anergy-inducing gene expression via TMEM20-mediated overexpression of intracellular Ca2+ concentration. In basal level, the miR-150 level is higher in naive CD8+ T cells than effector CD8+ T cells.

Activation or anergy formation is regulating by PMCA as main Ca2+ regulator in naïve CD8+ T cells. Whereas, other Ca2+ regulators also contribute to the Ca2+ regulation in effector CD8+ T cells to regulate the responsiveness of effector CD8+ T cells. Therefore, the anergy formation of naïve CD8+ T cells depend on the TMEM20 and it can be affected by miR-150 expression. As naïve CD8+ T cells are having higher level of miR-150, it may help it to maintain reproductive states in naive CD8+ T cells other than anergy state.

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