Published in final edited form as:

Crit Rev Immunol. 2017 ; 37(1): 39–58. doi:10.1615/CritRevImmunol.2018025213.

SLE-Associated Defects Promote Altered T Cell Function

José C. Crispín[a,*], **Christian M. Hedrich**[b,c], **Abel Suárez-Fueyo**[d,e], **Denis Comte**[d], and **George C. Tsokos**[e,f,*]

[a]Departamento de Inmunología y Reumatología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [b]Department of Women's & Children's Health, Institute of Translational Medicine, University of Liverpool, Liverpool, UK; [c]Department of Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust Hospital, Liverpool, UK; [d]Divisions of Immunology and Allergy, Lausanne University Hospital, Lausanne, Switzerland; [e]Department of Rheumatology, Beth Israel Deaconess Medical Center, Boston, USA; [f]Harvard Medical School, Boston, USA

Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease linked to profound defects in the function and phenotype of T lymphocytes. Here, we describe abnormal signaling pathways that have been documented in T cells from patients with SLE and discuss how they impact gene expression and immune function, in order to understand how they contribute to disease development and progression.

Keywords

autoimmunity; CREM; PP2A; SLAM; systemic lupus erythematosus; T cell

I. INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that primarily affects women.[1] It has a strong hereditary component and more than 40 loci have been identified in genome-wide association studies that confer risk for SLE development.[2] Although the mechanisms through which risk loci contribute to SLE are mostly unknown, the current paradigm proposes that environmental factors, for example infections and hormones, can trigger pathological behavior in genetically predisposed immune cells from patients with SLE.[3] According to that hypothesis, the presence of risk alleles would affect the response of immune cells to certain stimuli, promoting inflammation and autoimmunity. Along these lines, it is important to emphasize the fact that immune responses, in particular adaptive immune responses, changes along the years as the immune system "learns" from its encounters with the environment. Each immune response entails the expansion, functional

*Address all correspondence to: Dr. José C. Crispín, Departamento de Inmunología y Reumatología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Vasco de Quiroga 15, Mexico City 14080, Mexico; Tel.: 5255 5487 0900 ext. 2610, carlos.crispina@incmnsz.mx and Dr. George C. Tsokos, Department of Rheumatology, Beth Israel Deaconess Medical Center, 330 Brookline Ave, CLS-937, Boston, MA 02115, USA; Tel.: 617 735 4160, gtsokos@bidmc.harvard.edu.

differentiation, and contraction of T cell and B cell clones with a consequent remodeling of the memory repertoire. Years before the diagnosis is established, individuals that will eventually develop SLE, lose immune tolerance and mount a chronic autoimmune response that manifests by a gradual accumulation of self-reactive autoantibodies.[4] This response precedes and underlies clinical manifestations of the disease, as it provides the autoantibodies that will cause damage directly or as immune complexes, as well as the activated self-reactive T cells that will infiltrate target organs and orchestrate local chronic inflammation.

The phenotype and function of T cells isolated from patients with SLE has been studied extensively in search for clues to explain the pathogenesis of the disease and in an attempt to identify molecules that can serve as biomarkers and/or therapeutic targets.[5] These studies have revealed that, in the context of SLE, T cell function is severely compromised as a result of a large number of signaling aberrations that distort their gene expression profile and, consequently, their response to environmental stimuli. These alterations probably contribute to the pathogenesis of the disease by skewing the cellular immune response towards a pro-inflammatory state and by promoting responses of a larger magnitude and duration. In this review, we describe and discuss phenotypic and functional anomalies that affect T cell behavior in patients with SLE.

II. TCR SIGNALING IN SLE T CELLS

The response of T cells to activation during antigen presentation represents the integration of a large variety of signals received through the T cell receptor (TCR) and other surface molecules, including costimulatory molecules, cytokine receptors, and adhesion molecules. T cells from patients with SLE display quantitative and qualitative anomalies in their response to antigenic stimulation.[6] These are explained, at least in part, by a molecular modification in the TCR signaling pathway that has been named “TCR rewiring” (Fig.e 1).[7] In T cells from patients with SLE, the CD3ζ chain is expressed at abnormally low levels and its place is occupied by the Fcε receptor I γ (FcεRI γ) chain.[8] Various alterations, at the genetic, transcriptional, and mRNA and protein stability levels, have been shown to control CD3ζ expression and proposed to explain the CD3ζ defect observed in SLE T cells.

Intronic single-nucleotide polymorphisms (SNPs) in *CD247*, the gene that encodes CD3ζ, were typed in a large number of patients with SLE. A five-marker haplotype was associated with SLE, in particular in Asian patients.[9] How the SLE-associated alleles affect the expression of CD3ζ was not investigated. In an independent report, two different SNPs in the 3’UTR region of *CD247*, were also associated with SLE. Importantly, the presence of the SLE-associated alleles was shown to cause reduced expression of CD3ζ.[10] Together, these reports suggest that SLEassociated genetic variants can promote the reduced expression of CD3ζ, perhaps in response to specific stimuli, and thus promote the pro-inflammatory capacity of T cells.

Additional factors, have been identified in patients with SLE that may contribute to the downregulation of CD3ζ, in the first place, decreased transcription due to promoter hypermethylation[11] and altered transcription factor binding. Lower levels of

transcriptionallyactive Elf-1 (E-74-like factor)[12] and the c-AMP responsive element binding protein (CREB), as well as increased activity of the repressor cAMP response element modulator (CREM)α,[13] have been associated with decreased CD3ζ transcription in patients with SLE. Another important mechanism is the generation of unstable isoforms due to alternative splicing. T cells from SLE patients present a defect in the levels of the alternative splicing factor/splicing factor 2 (ASF/SF2),[14] and this protein limits the production of unstable alternative spliced CD3ζ isoforms.[15] As a result, SLE T cells contain increased levels of an unstable CD3ζ variant that lacks two critical regulatory adenosine/uridine-rich elements (ARE) and a translation regulatory sequence that are located within a region that is deleted during splicing (nucleotides 672–1233 of the transcript).[16] As a consequence, transcript stability and translation of this isoform are significantly lower than the isoform generated in the presence of normal levels of ASF/SF2.[17,18] Finally, increased Caspase 3 activity in SLE T cells has been associated with enhanced proteolysis of CD3ζ. In concordance, treatment with the small molecule DEVD, a Caspase 3 inhibitor, restores CD3ζ levels in SLE T cells.[19]

CD3ζ depletion or downregulation of its signaling pathway leads to autoimmune and inflammatory conditions in mice.[20,21] This has been proposed to occur because CD3ζ depletion lowers the TCR activation threshold, which impairs selection of thymic regulatory T cells (Tregs), while allowing self-reactive T cells to escape negative selection.[20] Additionally, downregulation of CD3ζ promotes the differentiation of T cells towards an activated/memory phenotype that is characterized by the expression of IFN-γ but not IL-2.[21,22]. This relationship between CD3ζ levels and cytokine polarization has also been observed in T cells from SLE patients where a negative correlation has been described between CD3ζ levels and IFN-γ production.[23]

Defective activation of Elf-1, that is in part due to increased activity of protein phosphatase 2A (PP2A)[24] also promotes the ectopic expression of FcεRIγ, because Elf-1 represses the transcription of *FCER1A*.[25] While CD3ζ signals through Zeta chain associated protein (ZAP)70, FcεRIγ binds and activates spleen tyrosine kinase (Syk). Syk possesses a greater enzymatic capacity as compared to Zap70,[26] and induces a strong calcium signaling through the activation of LAT, and PLCγ, which produce IP_3, and a fast f-actin polarization through Vav under TCR stimulation.[27] These defects can be reversed by forced expression of CD3ζ.[28]

In addition to TCR rewiring, SLE T cells present increased numbers of pre-clustered lipid rafts, as indicated by the increased presence of the ganglioside GM1, and a different protein composition of these rafts.[29,30] In particular, lipid rafts in SLE T cells exhibit an accumulation of CD45 and Lck[29] in addition to including FcεRIγ, Syk and PLCγ.[30] The proximity of these molecules in a pre-clustered raft may contribute to the hyperactivation of SLE T cells which translates into increased calcium flux and reorganization of the cytoskeleton. The importance of lipid rafts in SLE pathology was demonstrated by inhibiting glycosphingolipid (GSL) biosynthesis in vitro. This intervention normalized GSL metabolism and corrected $CD4^+$ T cell signaling and functional defects.[29,31] Additionally, enhancing lipid raft aggregation in T cells from lupus-prone mice (MRL/*lpr*) accelerated disease, while the disruption of lipid raft aggregation delayed disease.[32]

Aforementioned alterations modify the TCR threshold and, therefore, T cell responses to antigens. After activation, normal T cells produce IL-2, however, due to the rewiring of the TCR and to the increased calcium signal, SLE T cells display a defect in IL-2 expression. Increased tyrosine kinase phosphorylation and intracellular calcium, promoted by FcεRIγ/Syk signaling, lead to early degradation of LAT.[33] This disruptis the signaling through extracellular signalregulated kinases (ERK)[34] which controls transcription and activation of c-FOS, one of the components of AP-1, a transcription factor essential for IL-2 transcription.[35] ERK activation is also downregulated by PP2A and protein tyrosine phosphatase SH2 domain–containing PTP (SHP2), whose activity is increased in SLE T cells.[36]

Increased calcium flux activates calcium/calmodulin-dependent protein kinase IV (CaMK4), which promotes the activation of CREMα, a transcription factor expressed at increased levels T cells from SLE patients (see below).[37,38] Additionally, the activity of CREB, a transcription factor that positively regulates the *IL2* promoter, is reduced in SLE T cells. Increased activity of PP2A, and the interaction of CREB with the PKA subunit RIIβ whose expression is increased in the nuclei of SLE T cells,[39] contribute to repressing CREB function.

Defective IL-2 production has many consequences. IL-2 is a key factor for T cell survival and expansion and its presence is necessary to make T cells susceptible to activation-induced cell death, which is impaired in SLE.[40] Another factor contributing to resistance to activation-induced cell death is the activation of the PI3K/AKT pathway.[41] Although the exact mechanisms resulting in increased PI3Kδ activity in SLE T cells has not been described, a possible explanation is the stronger signal transduction delivered by FcεRIγ/Syk in response to TCR activation.[42] Increased PI3K and CaMK4 activity,[43] together with abnormal mitochondria hyperpolarization leads to activated mammalian/mechanistic target of rapamycin (mTOR), a sensor of mithochondrial potential.[44] Increased mTOR activity enhances glycolysis and prevents autophagy, alters the epigenome in SLE T cells,[45] and promotes T cell differentiation towards pro-inflammatory subsets.[46] These alterations are believed to drive inflammation in SLE and, accordingly, inhibition of mTOR restores SLE T cell signaling and differentiation, in part by increasing CD3ζ expression,[47] both in humans and lupus-prone mice.[43,48,49]

III. THE CREM TRANSCRIPTION FACTOR SUPERFAMILY IN SLE

The transcription factor CREMα is expressed at increased levels in T cells from patients with SLE and centrally contributes to altered T cell function and tissue damage.[50,51] CREMα belongs to the CREM superfamily of transcription factors that comprises more than 50 known isoforms.[52] Members share a high degree of sequence homology, particularly within their DNA binding domains (a leucine zipper domain), and recruit to relatively common palindromic consensus elements (5'TGACGTCA3') that are referred to as cAMP responsive elements (CRE). Recruitment of CREM transcription factors can also occur at 5' half elements (5'TGAC3').[53] The name "CRE" is based on the observation that CREM is activated in response to cAMP. Hormones and growth factors induce cAMP generation through adenylate cyclase, which in turn promotes the activation of protein kinases,

including PKA, PKC, and casein kinases I and II. All of these activate CREM through phosphorylation. Alternatively, TCR activation and calcium influx activate protein kinases, subsequently resulting in the activation of CREM family transcription factors.[54,55]

A. The (Dys-)Regulation of CREM

The human *CREM* gene spans 14 exons encoding over 50 known alternative transcripts. The multitude of isoforms is achieved by the presence of alternative promoters and splicing variants.[52,53,56] Transcription of most CREM variants is controlled by two alternative promoters: promoter P1 upstream of exon 1, and P2 upstream of exon 2.[57,58] The short inducible cAMP early repressor (ICER) isoform, however, is controlled by an intronic promoter region within the 3' region of the CREM gene.[59,60]

Human T cells predominantly express the isoform CREMα, which is under the control of *CREM* promoter P1. Its expression is increased in T cells from patients with SLE.[50,51,61] Indeed, activity of P1 and resulting CREMα expression directly reflects disease activity in SLE patients.[50,51,58,61] Activity of P1 in SLE patients is promoted by increased expression and enzymatic activity of PP2A. PP2A dephosphorylates the transcription factor signaling protein (SP)1 at serine residue 59, which then recruits to P1 and mediates its *trans*-activation.[57,58] Since SP1 expression is increased in response to estrogen receptor engagement, this mechanisms may play a significant role in the female predominance of SLE.[62] Furthermore, the *CREM* promoter P1 exhibits reduced levels of CpG DNA methylation in T cells form SLE patients when compared to controls.[61] Methylation of CpG dinucleotides within the DNA sequence is a potent mechanisms preventing recruitment of transcription factors and other molecules of the transcriptional complex to regulatory regions.[63] Thus, reduced DNA methylation at P1 in T cells from SLE patients likely contributes to increased transcription factor recruitment and CREMα expression. Furthermore, the *CREM* promoter P1 undergoes epigenetic remodeling through histone H3 lysine 4 tri-methylation (H3K4me3), an activating epigenetic mark. Indeed, T cells from SLE patients exhibit increased H3K4me3 and reduced DNA methylation at the promoter P1 which is instructed by recruitment of the histone-lysine N-methyltransferase Set1 and subsequently reduced recruitment of DNMT3a.[64]

Other than P1, the alternative intronic *CREM* promoter P2 is under the control of the transcription factor AP-1. While activation of T cells from healthy individuals results in AP-1 recruitment to P2, this mechanisms is decreased in T cells from patients with SLE.[58] At least partially this is caused by the fact that expression of AP-1 (*FOS*) itself is regulated by CREMα, which may be responsible for the observation that CREMα expression in *ex vivo* isolated T cells from SLE patients is increased as compared to cells from healthy controls, but cannot be further upregulated through stimulation of the CD3-TCR complex.[58,65]

As mentioned above, CREMα requires activation by protein kinases. In the context of SLE, CaMK4 plays a significant role. CaMK4 is a multifunctional serine/threonine kinase that regulates gene expression and protein activation.[66] It is increased in T cells from SLE patients and lupus-prone MRL/*lpr* mice, where it contributes to increased expression of IL-17A and reduced expression of IL-2 through increased phosphorylation of CREMα.

[38,43,67] Thus, CaMK4 is involved in the generation of effector phenotypes in SLE T cells that are characterized by increased IL-17A and reduced IL-2 expression. In addition to reduced activation of CREMα, CaMK4 inhibition restored previously increased activation of the AKT/mTOR pathway, which is centrally involved in the differentiation of Th17 cells.[43] In agreement with the aforementioned effects of CREMα on the *IL17A* and *IL2* genes, inhibition or deletion of CaMK4 in lupus-prone MRL/*lpr* mice restored IL-2 and IL-17A expression.[38,43,68,69]

Taken together, altered activation of protein kinases (CaMK4) and phosphatases (PP2A), impaired expression and activation of transcription factors (CREMα itself, SP1, and AP-1) and reduced DNA methylation at the CREM promoter P1 favor CREMα expression in T cells from SLE patients.

B. CREM and ICER Contribute to T cell Dysregulation in SLE

In T cells, both CREMα and the short Inducible cAMP early repressor (ICER) isoform act as transcriptional regulators with complex function. While CREMα and ICER repress some genes, they activate others (Table 1).[70–93]

In $CD4^+$ T cells from SLE patients, CREMα centrally contributes to imbalanced expression of IL-2 and IL-17A.[52,61,63,70–75] CREMα is recruited to a regulatory element in the *IL2* proximal promoter where it mediates *trans*-repression and epigenetic remodeling through its interaction with histone deacetylase HDAC1 and DNA methyltransferase DNMT3a.[12,30,32] These interactions mediate histone de-acetylation, and increased DNA methylation, two potent epigenetic mechanisms resulting in chromatin condensation and subsequently reduced gene expression. In addition to orchestrating direct regulatory events at the *IL2* promoter, CREMα indirectly affects IL-2 expression through the *trans*-repression of AP-1, which under physiological conditions activates IL-2 expression.[65] Conversely, CREMα induces epigenetic “opening” of the *IL17* gene cluster, comprising the homologues *IL17A* and *IL17F*.[61,70] Both cytokines, IL-17A and IL-17F, are potent pro-inflammatory mediators. Increased expression of IL-17A has been linked with several autoimmune/inflammatory conditions, including SLE, rheumatoid arthritis, psoriasis, and others. CREMα recruits to both the *IL17A* and *IL17F* proximal promoter in T cells from SLE patients.[70,71] In contrast to what is observed at the *IL2* locus, CREMα fails to recruit DNMT3a and HDAC1 to the *IL17* cluster, while it actually induces DNA demethylation and increased histone acetylation[61,70,71] The exact mechanism that explains this differential behavior is currently unknown. However, this observation is in agreement with observations in male germ cells, where the CREM isoform CREMτ mediates histone H3 acetylation.[76] The observation that CREMα interacts with the histone acetyltransferase p300 may be of special interest in this context.[74] While CREMα recruits p300 to the *IL2* promoter, where p300 fails to be activated, the different transcription factor microenvironment at the *IL17* cluster may allow for p300 activation and subsequent histone acetylation.[74,77] Since p300 can physically and functionally link transcription factors, and since interactions with signal transducer and activator of transcription (Stat) family transcription factors mediate histone acetylation through p300,[78] a functional interaction between CREMα and Stat3 at *IL17A* appears likely, however, currently remains to be experimentally proven (Fig. 2).

While CREMα was previously known as a transcriptional repressor, it *trans*-activates the *IL17A* proximal promoter thereby contributing to increased IL-17A expression.[61,70] In contrast to increased IL-17A expression, the isoform IL-17F is expressed at reduced levels in T cells from patients with SLE as compared to healthy controls.[71] This may enhance the pro-inflammatory phenotype of T cells, because IL-17A and IL-17F form heterodimers, which are of less inflammatory potency as compared to IL-17A homodimers that are increased in SLE T cells. Reduced IL-17F expression is (at least partially) caused by trans-repression of the *IL17F* proximal promoter by CREMα.[70,71]

Observations in human T cells are supported by data from transgenic animals. Forced expression of CREMα in mice results in autoimmune phenomena that are caused by reduced IL2 and increased IL-17A expression, and can (at least partially) be restored by the delivery of recombinant IL-2.[73,79] Furthermore, the generation of IL-17A-expressing Th17 cells depends on the pro-inflammatory cytokine IL-21. In CREMα transgenic animals, IL-21 expression is increased secondary to CREMα recruitment to the *IL21* proximal promoter resulting in *trans*-activation.[80]

Another contributor to the generation of Th17 cells and increased IL-17A expression may be the ICER isoform. Recently, also ICER has been demonstrated to be expressed at increased levels in T cells from SLE patients.[81] In T cells from wild-type mice, ICER is predominantly expressed in the Th17 compartment. T cells from CREM-deficient mice fail to differentiate to Th17 cells, while reconstitution of ICER expression was sufficient to correct this defect. Furthermore, CREM-deficient animals were protected from Th17-mediated autoimmune/inflammatory disease including anti-glomerular basement membrane-induced glomerulonephritis and experimental encephalomyelitis.[81] Since IL-17A-producing effector T cells fail to produce IL-2,[61] the observation that ICER, in analogy to CREMα, also *trans*represses the *IL2* and *c-FOS* (AP1) promoters supports the involvement of this short isoform in effector T cell function and T cell pathology in SLE.[82,83] Taken together, these observations complement and confirm observations of CREMα effects in T cells from SLE patients and transgenic animals, and offer another CREM isoform (ICER) as potential contributor to altered T cell function in SLE.

$CD3^+TCR^+CD4^-CD8^-$ “double negative” (DN) T cells exhibit effector phenotypes and express IL-17A. In SLE patients, numbers of DN cells are increased in the peripheral blood and DN T cells infiltrate the kidneys during lupus nephritis, where they produce IL-17A and contribute to tissue damage.[84,85] DN T cells can derive from $CD8^+$ T cells through the downregulation of surface CD8 co-receptor expression.[85–88] CREMα may play a central role in this process, since it recruits to conserved elements within the *CD8* cluster. Indeed, CREMα *trans*represses the *CD8B* promoter and co-recruits DNMT3a and histone methyltransferase G9a to regulatory elements within the *CD8* cluster instructing epigenetic silencing and down-regulation of *CD8A* and *CD8B* expression.[86,87] These mechanisms are involved in the peripheral generation of DN T cells in healthy individuals, and to a higher extent, in SLE patients and lupus-prone MRL/*lpr* mice.

In addition to the aforementioned cytokines, CREMα is involved in dysregulated expression of several genes involved in T cell function. One additional CREMα-mediated event further

increases IL-17A expression. The Notch receptor family participates in signal transduction between neighboring cells. Proteolytic cleavage of the receptor releases the intracellular domain, which is translocated to the nucleus where it can act as transcriptional regulator.[89–91] Notch signaling pathways are centrally involved in T cell lineage determination and function. T cells from SLE fail to express Notch-1, which is (at least partially) caused by *NOTCH1 trans*-repression through CREMα, and increased DNA and histone (H3K27me3) methylation of the proximal promoter region.[92] Failure to express Notch-1 is associated with increased IL-17A expression.[92] As mentioned above, T cells from SLE patients exhibit altered TCR arrangement with replacement of the physiologically present CD3ζ by FcεRIγ.[8] CREMα recruits to the *CD247* (CD3ζ) promoter where it mediates in *trans*-repression and epigenetic remodeling through the induction of histone deacetylation. Subsequent replacement of the CD3ζ chain has severe consequences for downstream signaling pathways. Though under physiological conditions CREMα acts as strong *trans*-repressor of the *SYK* proximal promoter, this mechanisms fails to regulate gene expression in T cells from SLE patients secondary to reduced histone acetylation at the repressor element preventing CREMα recruitment.[93]

IV. PP2A AS A REGULATOR OF T CELL FUNCTION

PP2A is an ubiquitously expressed serine/threonine phosphatase that regulates a large number of fundamental cellular processes including signaling pathways, cell cycle and apoptosis, and cellular motility.[94] As other serine/threonine phosphatases, PP2A is a heterotrimer formed by the assembly of a scaffold subunit (PP2A A), a regulatory subunit (PP2A B), and a catalytic subunit (PP2A C). Two genes encode two homologous scaffold subunits (*PPP2R1A* and *PPP2R1B* encode PP2A Aα and β, respectively), and two genes encode two homologous catalytic subunits (*PPP2CA* and *PPP2CB* encode PP2A Cα and β). The products of these genes form core heterodimers (PP2A A/C) that are widely expressed and whose activities are regulated by posttranslational modifications and by the association of the third component, the regulatory subunit (PP2A B). At least 17 different proteins can act as PP2A regulatory subunits and their genes have been classified in four families: B (B55), B' (B56), B" (PR72/130), and B"' (Striatins).[95] Regulatory subunits associate with the PP2A A/C heterodimer in a mutually exclusive manner and determine the subcellular location of the enzyme and its specificity.[96]

Because PP2A is a known regulator of the transcriptional activity of CREB (see above)[97] and CREB is activity dampened in T cells from SLE patients, the levels and activity of PP2A were assessed in SLE T cells. Levels and enzymatic activity of the catalytic subunit (PP2A C) were found to be significantly increased in T cells from patients with SLE.[37] Overexpression was associated to decreased CREB transcriptional activity and impaired IL-2 production,[37] suggesting that the dysregulation possessed a pathogenic significance. In order to test that hypothesis, a transgenic mouse that expresses increased amounts of PP2A C in T cells was generated.[98] This system allowed the analysis of effects of increased T cell PP2A C in an otherwise normal immune system in a non-autoimmune background (C57BL/6). Transgenic mice did not spontaneously develop disease indicating that increased expression/activity of PP2A C in T cells alone does not lead to immune tolerance failure. However, when mice were challenged with a nephrotoxic serum that induces a non-severe

glomerulonephritis in the C57BL/6 background,[99] the transgenic mice developed intense glomerular inflammation and accelerated renal disease when compared to wild-type littermates.[98] The increased susceptibility to inflammatory disease depends on an unrestrained capacity to produce IL-17. In fact, IL-17 blockade abolished the phenotype and restored the resistance to glomerulonephritis to levels similar to those of wild-type mice.[98] This demonstrated that in an *in vivo* system, dysregulation of PP2A C could indeed affect T cell behavior and augment susceptibility to immune-mediated insults. It also highlighted the fact that certain molecular anomalies may affect pathology independently of their effects on immune tolerance.

Ex vivo isolated $CD4^+$ T cells from PP2A C transgenic mice produce IL-17 without previous cytokine-driven differentiation into Th17 cells.[98] In order to determine the extent to which increased PP2A C activity in T cells affects gene expression, microarray analyses were used to compare the transcriptome of PP2A C transgenic T cells and their wild-type counterparts.[100] PP2A C dysregulation caused increased expression of a limited number of genes; gene ontology analyses indicated that the perturbed transcripts were significantly enriched in inflammatory response genes.[100] This suggests that PP2A regulation in T cells is intimately involved in the modulation of the inflammatory capacity of the T cell. The *Il17* locus was further analyzed and chromatin immunoprecipitation (ChIP) experiments demonstrated that PP2A C overexpression was associated with local epigenetic changes that increased the accessibility of the *Il17* locus to transcription factors in such a manner that non-polarizing CD4 T cell activation promoted IL-17 production.[100] Importantly, the epigenetic landscape associated with increased PP2A C function was analogous to the one observed in CD4 T cells of patients with SLE,[70,100] suggesting that the increased production of IL-17 by T cells from patients with SLE may be influenced by epigenetic abnormalities that result from PP2A and CREMα dysregulation.

As mentioned earlier, PP2A represents a family of phosphatases that share a scaffold/catalytic core. Therefore, effects of increased PP2A C activity are difficult to conceptualize from a mechanistic point of view. Open questions include: Does the SLEassociated increase in PP2A C levels facilitate in a general manner the activity of PP2A? Alternatively, are certain functions selectively promoted?

T cells express all PP2A regulatory subunits[101] but only a few papers have analyzed their function. In these, PP2A regulatory subunits are shown to play an inhibitory role on T cell function.[101–103] This contrasts with the findings of the studies that have analyzed effects of PP2A C overexpression, which implicate the phosphatase as pro-inflammatory.[98,100] PP2A B56α regulates the accumulation of c-Myc, a key regulator of cell cycle and metabolic reprogramming in activated T cells.[104] B56γ, suppresses the activity of the transcription factor NF-κB in T cells activated through the TCR.[102] PP2A B55β is induced in activated T cells by cytokine withdrawal and its expression is necessary for T cells to undergo apoptosis in response to IL-2 deprivation. Interestingly, induction of this isoform is impaired in T cells from patients with SLE and the defect is strongly associated to resistance to apoptosis.[101] How defective induction of B55β in SLE T cells is related to the excessive expression of the catalytic subunit remains unknown.

Regulatory T cells (Treg) display higher PP2A activity as compared to conventional $CD4^+$ T cells.[105] In Treg, PP2A constitutively inhibits the mTORC1 complex that is necessary to maintain their suppressive capacity. This is achieved because FoxP3 induces the transcription of high levels of *Sgms1*, the gene that encodes for sphingomyelin synthase 1, an enzyme that maintains high intracellular levels of ceramide species that, in turn, inactivate the PP2A inhibitor SET.[105] This mechanism allows PP2A to avoid the TCR-mediated inhibition that occurs in conventional $CD4^+$ T cells (Fig. 3). mTORC1 inhibition is fundamental for Tregs to remain suppressive, because a Treg-specific deletion of the PP2A scaffold subunit (PP2A Aα) that impaired PP2A-mediated mTORC1 inhibition, abolished regulatory function and caused a lethal autoimmune inflammatory disease.[105]

These data highlight the complex and important roles that PP2A plays in T cell biology and illustrate how defects in the expression and/or activity of different components of the PP2A holoenzyme may contribute to altered T cell behavior and, in some instances, to the development of immune-mediated diseases.

V. SIGNALING LYMPHOCYTIC ACTIVATION MOLECULES (SLAM)

A. SLAMF Receptors on SLE T Cells

T cell proliferation and differentiation request multiple molecular interactions that occur between T cells and an antigen-presenting cells (APC). Interactions include (i) antigen recognition, (ii) engagement of co-regulatory molecules (co-stimulatory or co-inhibitory) and (iii) effects of soluble factors such as cytokines.[106,107] Co-regulatory molecules include well-characterized protein interactions such as binding of B7–1 (CD80) or B7–2 (CD86), which are expressed on activated APC, to the T cell surface co-receptor CD28 on T cells. Downstream signaling pathways of CD28 provide co-stimulatory signals for T cell survival, proliferation and differentiation. Other receptors belonging to the CD28 family are expressed on the T cell surface and act as co-activating (ICOS) or co-inhibitory receptors. As an example, cytotoxic T lymphocyte antigen-4 (CTLA-4) acts as a competitive inhibitor of CD28 during T cell activation. In that setting, SLAMF receptors have emerged lately as important regulatory molecules involved in T cell survival, proliferation and differentiation.

SLAMF (signaling lymphocytic activation molecule family) is a family of immunoregulatory receptors expressed predominantly on hematopoietic cells, where they act as immune system co-regulatory molecules. They deliver downstream signals upon their engagement to modulate magnitude of the immune response.[108,109] They are type I transmembrane glycoproteins belonging to the CD2 superfamily of immunoglobulin domaincontaining molecules.[108,109]

The SLAMF family is composed of seven molecules encoded in the *SLAMF* gene cluster: SLAMF1 (CD150, SLAM), SLAMF2 (CD48), SLAMF3 (CD229, Ly9), SLAMF4 (CD244, 2B4), SLAMF5 (CD84), SLAMF6 (CD352, NTBA, Ly108), SLAMF7 (CD319, CS1, CRACC). Two other molecules, SLAMF8 (CD353, BLAME) and SLAMF9 (CD84-H1) are located outside, but in close proximity to the *SLAMF* gene cluster.[110] Structurally, SLAMF molecules are composed of an extracellular region, which contains one variable (V)-Ig like and one constant (C2)-Ig like domain, while SLAMF3 is composed of four Ig-like domains

(2 tandems repeats of V-like regions and C2-like regions). A unique feature of the SLAMF members is that they act as self-ligands as they interact in a homotypic manner, apart from SLAMF2 that associates with SLAMF4.

SLAMF2 is a glycophosphatidylinositol (GPI)-anchored molecule that lacks a cytoplasmic domain. The other members of the co-receptor family, with the exception of SLAMF9, contain a cytoplasmic domain characterized by the presence of one to four intracellular switch motif amino acid sequences (ITSM). Upon SLAMF engagement, the ITSM sequence recruits its adaptor molecules SLAM-associated protein (SAP) or Ewing's sarcoma's/FLI1-activated transcript 2 (EAT-2) to mediate downstream signaling.[108]

The role of SLAMF receptors in autoimmunity, and more specifically in SLE, has been suggested by different studies in mice and humans. The *SLAMF* gene cluster is located within chromosomal region 1q23, a region that has been associated with SLE susceptibility in genomewide association studies (GWAS).[111,112] Moreover, the 1H3 genomic region in mice, synthenic to human 1q23, has been associated with lupus manifestations in three different mouse models of spontaneous autoimmunity: NZB/W F1, NZM, and BXSB.[113–115] In addition, SNPs and *SLAMF* variants have been associated to clinical manifestations of SLE and to other autoimmune diseases such as rheumatoid arthritis.[116–119]

Several studies have examined the expression of SLAMF1 to 7 receptors on the surface of T cells isolated from the peripheral blood of SLE patients in comparison to healthy controls, and delivered variable results, thus reflecting the heterogeneity of the disease.[120–127] Two studies systematically examined the expression of SLAMF1 to 7 receptors on the T cells from cohorts of patients suffering from SLE.[120,121] In one, authors examined the expression of SLAMF receptors on T cells isolated from patients with lupus nephritis and showed that expression of SLAMF3, SLAMF5, and SLAMF7, on $CD8^+$ and DN T cells was lower in patients who are in remission as compared to patients with active nephritis.[121] In another study, the expression of SLAMF1 to 7 receptors was assessed in the peripheral blood of patients with SLE in different $CD4^+$ and $CD8^+$ T cell subsets (i.e. naïve, central memory, and effector memory $CD4^+$ T cells and naive, central memory, effector memory, and terminally differentiated memory $CD8^+$ T cells).[120] The authors showed that SLAMF1 expression is increased on SLE T cells, whereas the frequency of SLAMF4 and SLAMF7, which are mainly expressed on memory $CD8^+$ T cells, is decreased in comparison to healthy controls.[120]

B. SLAMF1

SLAMF1 is mainly expressed on memory $CD4^+$ and $CD8^+$ T cells. Its expression is increased on SLE T cells as compared to healthy controls.[120,122] Few data are available on the function of SLAMF1 in SLE T cells. In one study, authors examined the role of SLAMF1 engagement on regulatory T cells and showed that an anti-SLAMF1 agonist monoclonal antibody increased their suppressive function.[122]

C. SLAMF3

SLAMF3 shows a high level of expression on $CD4^+$, $CD8^+$ and DN T cells independently of their level of differentiation from naïve to effector memory (or terminally differentiated

effector memory) $CD8^+$ T cells.[120,123] However, differences in the expression levels between T cells isolated from SLE and controls are minimal, with only a slightly increased expression on naïve $CD4^+$ and $CD8^+$ T cells from SLE patients.[120,123]

SLE is characterized by a compromised IL-2 availability and production.[40] Recently, it has been proposed that not only IL-2 production but also IL-2 signaling pathways are impaired in SLE $CD4^+$ T cells. This is illustrated by decreased JAK3 phosphorylation, STAT5 phosphorylation, and proliferation in response to exogenous IL-2 in SLE patients when compared to healthy controls.[124–128] In this context, SLAMF3 engagement with a specific monoclonal antibody has been shown to restore the sensitivity of $CD4^+$ T cells to IL-2. The process is mediated through the up-regulation of the IL-2 receptor alpha (CD25) on the cell surface in response to SLAMF3 engagement, through a mechanism involving phosphorylation of the transcription factor Smad3.[123] Moreover, activation of naïve $CD4^+$ T cells with a monoclonal antibody directed against SLAMF3 promotes helper T cell differentiation toward a suppressive phenotype, while inhibiting Th1, Th2 and Th17 differentiation.[123] Recent studies indicated that low-dose IL-2 treatment can be beneficial in SLE patients.[129–131] Effects of IL-2 are mediated through increased numbers of regulatory T cells.[132] In this context, an SLAM3 agonistic agent, which enhances the response of $CD4^+$ T cells to IL-2, may potentially offer further support in therapeutic use of IL-2, especially in patients who do not tolerate IL-2 treatment or who display resistance to low dose IL-2 injections.

D. SLAMF4

SLAMF4 expression is decreased in SLE patients as compared to healthy controls. This coreceptor is mainly expressed on $CD8^+$ and DN T cells. SLAMF4 expression increases as $CD8^+$ T cells differentiate from naïve to effector phenotypes, whereas its level of expression on $CD4^+$ T cells remains low, even after cell activation.[120,124] It has been proposed that the relative increase of $SLAMF4^-$ $CD8^+$ T cells observed in SLE is related to the expansion of DN T cells that are involved in SLE immunopathogenesis.[124]

E. SLAMF6

In most studies, no difference in the expression of SLAMF6 has been observed between SLE and healthy controls.[120,121] In a small cohort of SLE patients, in whom expression of SLAMF6 was up-regulated, ligation of anti-SLAMF6 monoclonal antibody has been linked with increased Th1 and Th17 cytokine production.[126,127,133] Further studies are warranted on larger cohorts of SLE patients to definitely establish the role of SLAMF6 engagement in SLE.

F. SLAMF7

The role of SLAMF7 was mainly studied in patients with multiple myeloma, where ligation of SLAMF7, with a specific monoclonal antibody has been suggested to promote NK cytotoxicity and antibody-dependent cell-mediated cytotoxicity directed against tumor cells.[134,135] Few data are available on SLAMF7 in SLE and studies mainly focused on T cells and not on NK cells.[120,121,136] As with SLAMF4, SLAMF7 is mainly expressed on $CD8^+$ and DN T cells, and its expression defines $CD8^+$ T cells with an effector phenotype and function.

Its expression levels are significantly lower in SLE patients as compared to healthy controls. Recent data emphasize that ligation of SLAMF7 with a monoclonal antibody may be of interest in SLE, as it enhances anti-viral CD8 cytotoxic immune responses, restoring them to physiological levels. SLAMF7 expression and function of SLE NK cells has not been evaluated yet.

G. SAP

Upon engagement, SLAMF receptors interact with SAP (SLAM associated protein, SH2D1A), a highly conserved cytoplasmic SH2-domain-containing molecule, which is expressed in T cells, NK cells, NKT cells, eosinophils and platelets.

Absence of SAP results in a rare primary immunodeficiency known as XLP (X-linked lymphoproliferative disease). XLP is a disease in which patients develop a fulminant lymphoproliferation in response to EBV infection.[137]

As compared to healthy controls, reduced expression of SAP has been observed in T cell subsets isolated from the peripheral blood of SLE patients.[138] Moreover, a link has been established between reduced SAP expression, early signaling defects, and reduced IL-2 production in T cells, important features of SLE.[138] In light of these observations, treatments aiming at restoring SAP expression or activity have been suggested as potential therapeutic targets in SLE.

Overall, our current understanding of SLAMF and SAP in T cells strongly suggest a role of these molecules in the immunopathogenesis of SLE. However, more investigation is warranted to better understand how these molecules act together. An important aspect will be to assess the expression of all SLAMF molecules on the same T cell to better understand their interaction. As an example, a better characterization of SLAMF4 and SLAMF7 on differentiated $CD8^+$ T cell subsets would be of interest to understand whether these molecules delineate different functional subsets of cytotoxic effector lymphocytes. Moreover, further characterization of SLAM receptor on other hematopoietic cells involved in the immune response (B cells, NK cells, NKT cells, innate lymphoid cells, etc.) is mandatory in autoimmunity. Understanding the exact role of SLAMF cell surface co-receptors may deliver new therapeutic targets in SLE and other autoimmune/inflammatory disorders. *In vitro* studies have shown that SLAMF3 engagement, with an anti-SLAMF3 specific monoclonal antibody restores responsiveness of $CD4^+$ T cells to IL-2, and favors Treg differentiation, while SLAMF7 engagement enhances $CD8^+$ T cell degranulation and cytotoxic response to viral antigens.

VI. CONCLUSIONS

We have described and discussed phenotypic and functional anomalies that have been documented in T cells from patients with SLE. From a general point of view, it is evident that the behavior of T cells isolated from patients with SLE is abnormal. However, how these changes are related to the disease in general, and to one another remains, in most cases, an unresolved matter.

T lymphocytes are equipped with a large array of receptors that allow them to “sense” the environment and their *raison d’etre* is to adapt their behavior and that of surrounding cells to the prevalent stimuli. Therefore, the analysis of T cells from patients with SLE at a cellular and/or molecular level is challenging because the disease itself affects the expression of genes and proteins and modifies the behavior of cells. On the other hand, some anomalies may represent effects of SLE-associated genetic variants. Therefore, the phenotype of SLE T cells probably represents a complex combination of preexisting anomalies and defects acquired through chronic immune activation and exposure to inflammatory mediators.

It is likely that abnormal T cell behaviors described in this review exert an impact on disease development and progression. Aside from whether the defects represent primary or secondary alterations, their presence is expected to affect T cell functions during steady state and in the process of productive immune responses. However, to date many questions remain unanswered. In particular, the pathogenic contribution of defects and their functional relationship remains unclear. A deeper understanding of T cell function in health and disease will aid in gaining a better understanding of the nature of the disease, and allow for the introduction of individualized and target-directed therapies.

ACKNOWLEDGMENTS

Part of the work summarized in this review was funded by CONACYT grants Fronteras de la Ciencia 2015 (549), Ciencia Básica 2015 (256752), and FOSISS 2016 (272118) to J.C.C. C.M.H. was supported by the Fritz-Thyssen-Foundation, the intramural MeDDrive program of TU Dresden, the Foundation for Therapeutic Research, and research support by Novartis Pharmaceuticals. A.S.F. is funded by NIH, grant T32 AI074549.

ABBREVIATIONS:

AP-1	activator protein 1
APC	antigen-presenting cell
ARE	adenosine/uridine-rich elements
ASF	alternative splicing factor
CaMK4	calcium/calmodulindependent protein kinase IV
ChIP	chromatin immunoprecipitation
CRE	cAMP responsive elements
CREB	c-AMP responsive element binding protein
CREMα	cAMP response element modulator α
CTLA-4	cytotoxic T lymphocyte antigen-4
DN	double negative
DNMT	DNA methyltransferase
EAT-2	Ewing’s sarcoma’s/FLI1-activated transcript 2

Elf-1	E-74-like factor
ERK	extracellular signal-regulated kinases
FcεRI γ	Fcε receptor I γ chain
GPI	glycophosphatidylinositol
GSL	glycosphingolipid
GWAS	genome-wide association studies
HDAC	histone deacetylase
H3K4me3	histone H3 lysine 4 tri-methylation
ICER	inducible cAMP early repressor
ICOS	inducible costimulatory
IFN	interferon
IL	interleukin
IP_3	inositol 1,4,5-trisphosphate
LAT	linker for activation of T cells
mTOR	mammalian/mechanistic target of rapamycin
PI3K	phosphatidylinositol-4,5-bisphosphate 3kinase
PKA	protein kinase A
PLC	phospholipase C
PP2A	protein phosphatase 2A
SAP	SLAM associated protein
SF2	splicing factor 2
SHP2	protein tyrosine phosphatase SH2 domain–containing tyrosine-protein phosphatase
SLAM	signaling lymphocytic activation molecules
SLAMF	signaling lymphocytic activation molecules family
SLE	systemic lupus erythematosus
SNP	single-nucleotide polymorphism
SP1	signaling protein 1
Syk	spleen tyrosine kinase

TCR	T cell receptor
Treg	regulatory T cell
UTR	untranslated region
XLP	X-linked lymphoproliferative disease
ZAP-70	zeta chain associated protein 70

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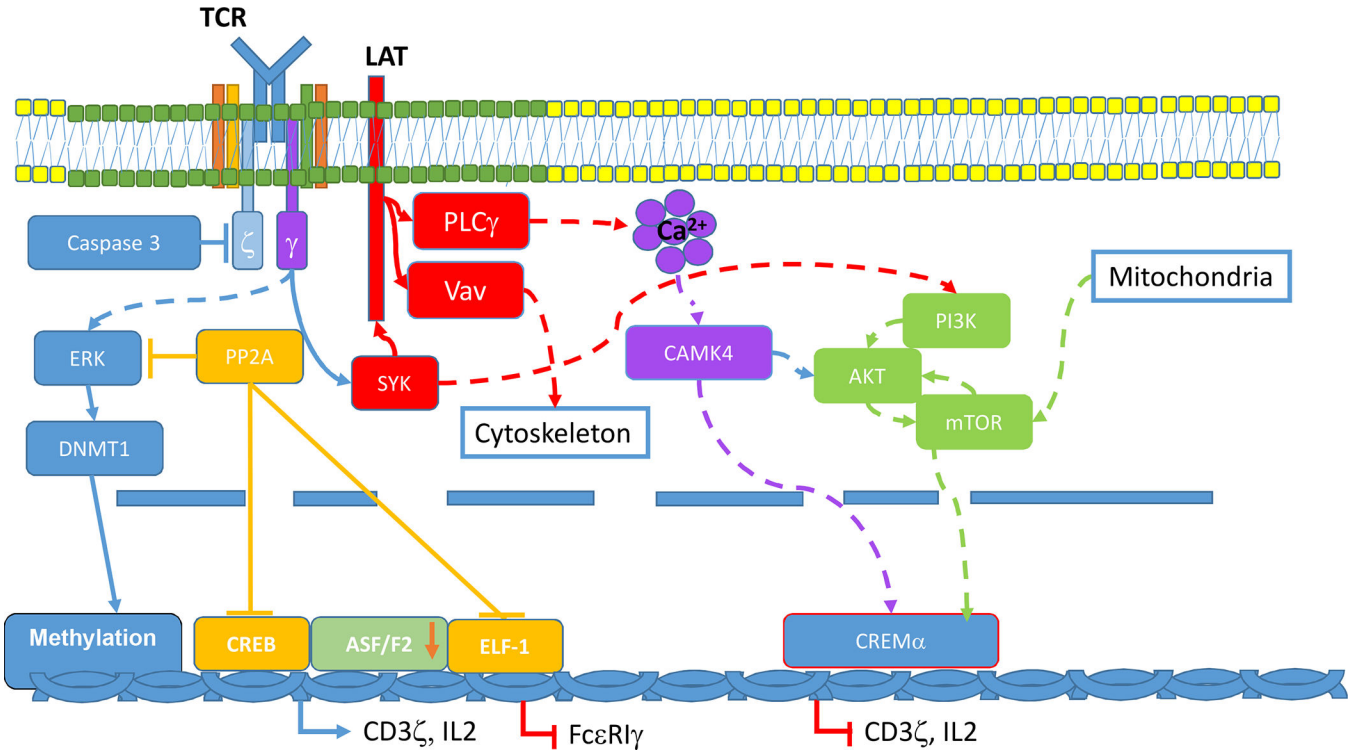

FIG. 1:

TCR rewiring in SLE T cells. Several alterations at the genetic and molecular levels contribute to decreased expression of CD3ζ and increased expression of FcεRIγ. These changes facilitate the activation of Syk, in place of canonical Zap70. The net result are T cells with lower activation thresholds that exert increased pro-inflammatory activities.

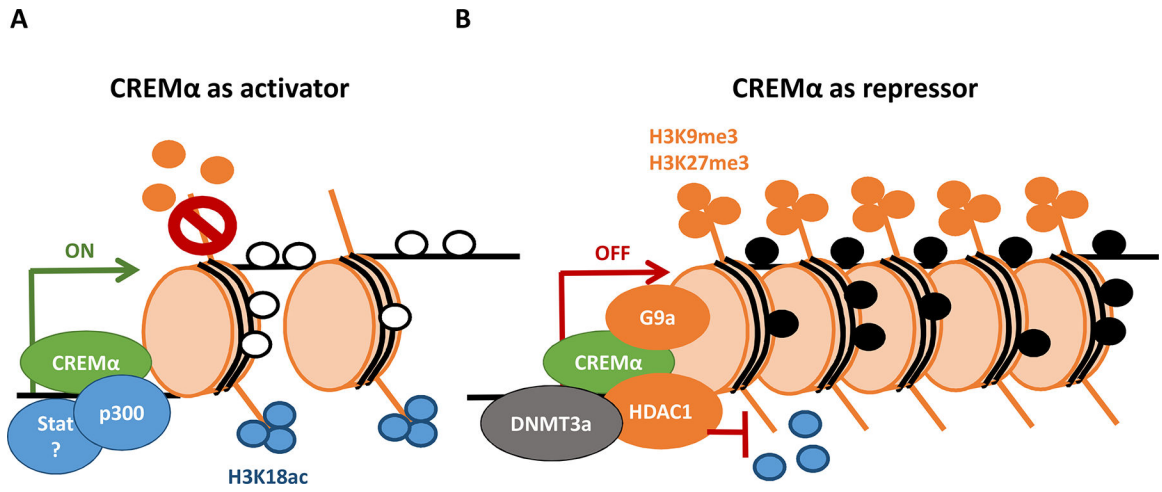

FIG. 2:

Effects of CREMα on gene expression. A) CREMα instructs *trans*-activation of the *IL17A* promoter and induces epigenetic "opening" by promoting histone acetylation (H3K18ac, blue filled circles) and DNA demethylation (black open circles). Interactions with the transcriptional co-activator p300 and other transcription factors, such as STAT transcription factors, appear likely but have not been experimentally proved. B) Conversely, CREMα can instruct *trans*-repression of other promoters (*IL2, CD8A/B, NOTCH1,* etc.) and induce epigenetic "silencing" through the instruction of histone tri-methylation (H3K9me3, H3K9me3, orange filled circles) by histone acetyltransferase G9a, and DNA methylation (black circles) by DNA methyltransferase (DNMT)3a. Interactions with histone deacetylase (HDAC)1 mediate histone de-acetylation.

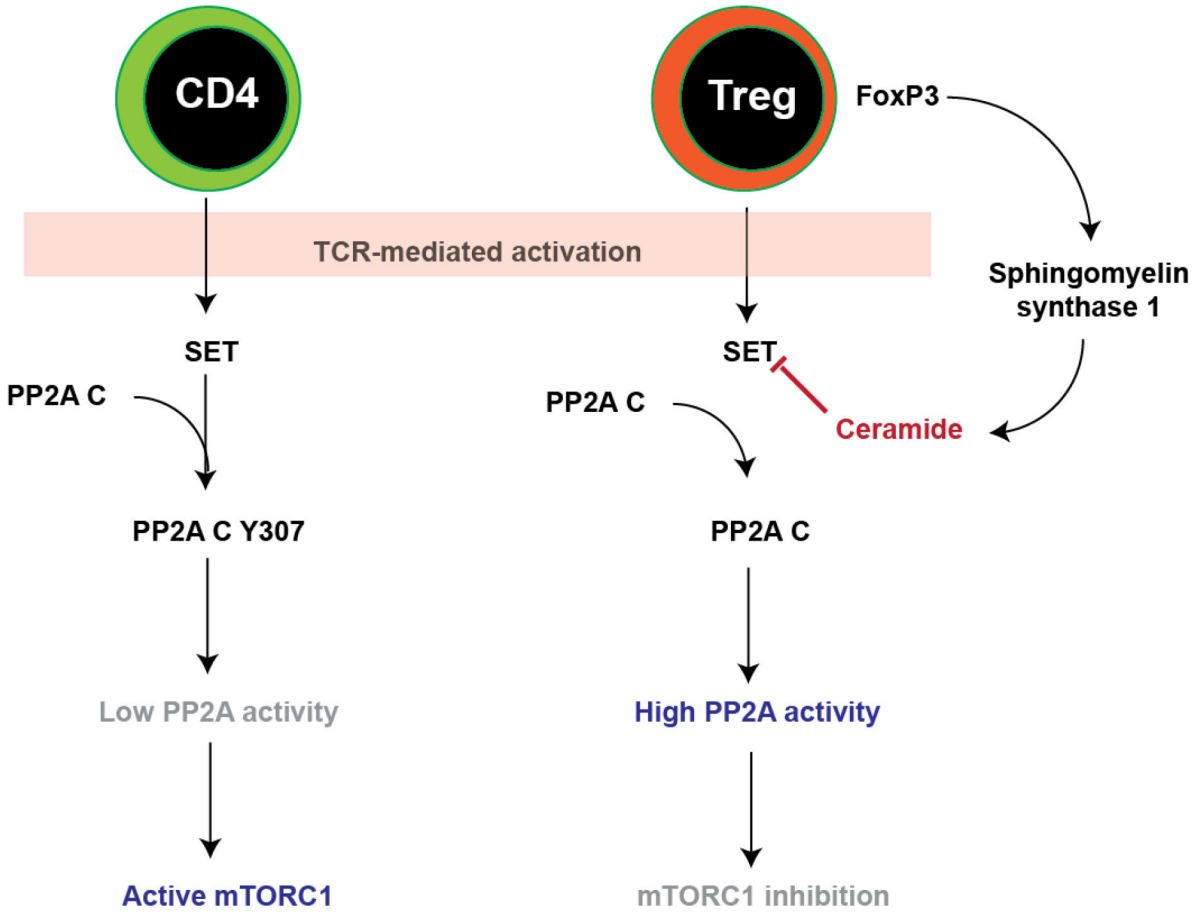

FIG. 3:

PP2A regulation in regulatory and conventional $CD4^+$ T cells. T cell activation induces the expression of SET, a molecule that mediates an inhibitory phosphorylation in PP2A C (Y307). This allows the activation of mTORC1. In regulatory T cells, high intracellular levels of ceramide impede the action of SET and thus protect PP2A from being inhibited. mTORC1 inhibition, maintained by high PP2A activity, is necessary for the suppressive function of Tregs.

Table 1:

Effects on CREMα and ICER on gene expression in T cells

Gene	Effect	Known Regulatory Mechanism	Isoform	Refs.
CD247 (CD3ζ)	↓	*Trans*-repression, epigenetic remodeling (histone deacetylation)	CREMα	13
CD8A and *CD8B*	↓	*Trans*-repression, epigenetic remodeling through DNMT3a, G9a	CREMα	86,87
FOS	↓	*Trans*-repression	CREMα	82
FOS	↓	*Trans*-repression	ICER	82
IL17A	↑	*Trans*-activation, epigenetic remodeling	CREMα	61,70
IL17A		*Trans*-repression	ICER	81
IL17F	↓	*Trans*-repression	CREMα	71
IL2	↓	*Trans*-repression, epigenetic remodeling through DNMT1, DNMT3a, HDAC1	CREMα	51,61,72–74
IL2	↓	*Trans*-repression	ICER	83
IL21	↑	*Trans*-activation	CREMα	80
NOTCH1	↓	*Trans*-repression, epigenetic remodeling (DNA methylation, H3K27me3)	CREMα	92
SYK	↓	*Trans*-repression; CREMα fails to recruit to Syk promoter in T cells from SLE patients because of altered CRE accessibility	CREMα	93