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T cells as therapeutic targets in SLE

José C. Crispín, Vasileios C. Kyttaris, Cox Terhorst, George C. Tsokos

Division of Rheumatology (J. C. Crispín, V. C. Kyttaris, G. C. Tsokos) and Division of Immunology (C. Terhorst), Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02115, USA.

Abstract

T cells contribute to the initiation and perpetuation of autoimmunity in systemic lupus erythematosus (SLE), and seem to be directly involved in the development of related organ pathology. Defects associated with CD8⁺ and T-regulatory (T_{REG}) cell function manifest in parallel with the expanded CD3⁺CD4⁺CD8[−] T cell lineage. The cytokine expression pattern is uniquely characterized by decreased expression of interleukin (IL)-2 and increased production of IL-17 and related cytokines. Therapeutic approaches that limit the cognate interaction between T cells and B cells, prevent inappropriate tissue homing and restore T_{REG} cell function and the normal cytokine milieu have been entertained. Biochemical characterization of SLE T cells has revealed distinct early and late signaling aberrations, and has enabled the identification of novel molecular targets that can be corrected with small molecules, and biomarkers that may foretell disease activity and predict organ damage.

Introduction

T cells in patients with systemic lupus erythematosus (SLE) display altered attributes and have an important role in disease progression and pathology. SLE T cells show inappropriate tissue homing and promote inflammation by secreting cytokines¹ and activating dendritic cells and B cells.² Although the precise circumstances that facilitate the ignition of SLE-related pathology remain mostly unknown, evidence indicates that, once tolerance is broken, T cells and B cells participate in the amplification and perpetuation of the autoimmune and inflammatory response.³ Both the cellular and humoral regulatory mechanisms fail to stop this process, while inflammation and tissue injury further contribute to the amplification and perpetuation of end-organ damage.⁴

Corticosteroids and immunosuppressive drugs are commonly used to treat patients with SLE. As indiscriminate suppressors of the immune-mediated inflammatory response, they mitigate pathology and clinical disease activity—albeit at the cost of considerable adverse effects. In this review, we present the advances made during the last decade that have shed light on the biochemical and molecular aberrations that lead to the characteristic cytokine production pattern and altered behavior of SLE T cells. These findings help us to understand

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Correspondence to: G. C. Tsokos, gtsokos@bidmc.harvard.edu.

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the nature of the SLE T cell, point to therapeutic targets that deserve further development, and identify additional, much-needed biomarkers in patients with SLE.

Cell signaling aberrations

T cells are equipped with a variety of receptors that enable them to acquire a comprehensive representation of the situation in which an antigen is being presented. According to signals delivered during its presentation, an antigen can elicit the differentiation of T lymphocytes into proinflammatory cells, T-regulatory (T_{REG}) cells, or quiescent, anergic T cells. The correct interpretation of external stimuli, such as cytokines and surface-bound molecules, is, therefore, central to the development of an appropriate response. This section discusses alterations to various aspects of T-cell signaling in SLE.

Altered CD3–TCR signaling

T cells from patients with SLE display faster and increased early signaling events upon engagement of the CD3–T cell receptor (TCR) complex (Figure 1 and Box 1).⁵ These events include an increase in intracellular calcium levels and phosphorylation of tyrosine residues in cytoplasmic proteins, which contribute to the abnormal function of SLE T cells. For example, increased intracellular calcium levels may lead to increased expression of CD40 ligand (CD40L) and increased levels of the transcriptional repressor CREM (cAMP response element modulator).^{6,7}

TCR rewiring

The altered calcium response has been shown to be a consequence of the reorganization of the proximal signaling machinery of SLE T cells.⁸ Levels of CD3 ζ , the principal signaling molecule in the CD3–TCR complex, are lower in T cells from patients with SLE than in those from healthy individuals.⁷ Decreased CD3 ζ levels are concomitant with the appearance of an analogous molecule, FcR γ (the common γ chain of the Fc ϵ receptor), which is normally scarce in T cells.⁹ Importantly, FcR γ partners with Syk (spleen tyrosine kinase) instead of with the normal signaling molecule ZAP-70 (ζ -chain-associated protein kinase 70);¹⁰ therefore, TCR-initiated signals are diverted, or ‘rewired’, and flow through different molecules, a consequence of which is the observed enhancement of the calcium response. The importance of the substitution of FcR γ for CD3 ζ has been demonstrated: forced expression of FcR γ increased the calcium influx in normal T cells,¹¹ whereas Syk inhibition corrected the calcium influx in SLE T cells.¹⁰

Key points

- Lipid raft clustering and a ‘rewired’ T-cell receptor lead to enhanced early signaling events in T cells from patients with systemic lupus erythematosus (SLE)
- Signaling aberrations cause altered gene transcription and produce a unique T-cell phenotype in SLE
- Increased numbers of CD3⁺CD4⁺CD8[−] T cells and interleukin (IL)-17-producing T cells, along with limited numbers of regulatory T cells, facilitate inflammation and perpetuation of autoimmunity in SLE
- Promising therapeutic targets include the interruption of T cell–B cell cognate interactions, restoration of IL-2 production, deletion of IL-17-producing T cells, and limitation of tissue infiltration by T cells

- Restoration of abnormally expressed signaling molecules results in the correction of effector T-cell function *in vitro* and may prove to be an effective and novel therapeutic approach

Aggregation of lipid rafts

Lipid rafts are cholesterol-rich areas of the membrane where signaling molecules accumulate at high density. Lipid raft clustering is evident in freshly isolated T cells from patients with SLE that have not been manipulated *in vitro*.^{12,13} signaling in T cells from patients with SLE is further facilitated by the clustering of lipid rafts, as cross-linking of the gangliosides present in lipid rafts prior to the engagement of the TCR further augments the signaling response.¹² the importance of this phenomenon is supported by the fact that a lipid-raft-clustering agent (cholera toxin) accelerated disease progression in a mouse model of lupus, whereas methyl- β -cyclodextrin, a substance that disrupts raft clustering, delayed the appearance of disease.¹⁴ accordingly, manipulation of lipid raft aggregation on SLE T cells might represent a process susceptible to therapeutic targeting.¹⁵

Increased T-cell death

Spontaneous apoptosis is increased in T cells from SLE patients.¹⁶ On the other hand, upon exposure to oxidizing agents, SLE T cells undergo necrosis rather than apoptosis.¹⁷ These abnormalities have been attributed to mitochondrial hyperpolarization and increased levels of reactive oxygen intermediates in T cells¹⁷—changes that alter the expression of redox-sensitive cytokines (such as interleukin [IL]-10 and tumor necrosis factor).¹⁸ Increased T-cell necrosis and apoptosis represents a source of nuclear material, which amplifies the inflammatory response in patients with SLE.

Elevated expression of CD44

Expression levels of CD44, a cell-surface molecule involved in cell adhesion, migration and signaling, are abnormally high in T cells from patients with SLE.^{12,19} Moreover, CD44 is found within aggregated lipid rafts along with its signaling partners, the ERM (ezrin, radixin and moesin) proteins (Figure 2). T cells with increased levels of phosphorylated ERM proteins are found in kidney infiltrates of patients with SLE,¹² suggesting that high expression levels of (and increased signaling through) CD44 facilitates the migration of SLE T cells into inflamed tissues. among the variant CD44 isoforms, CD44v3 and CD44v6 are increased in patients with SLE and correlate with disease activity and the presence of nephritis and anti-DNA antibodies.²⁰ Accordingly, CD44v3 and CD44v6 might serve as markers of organ involvement and disease activity.

Altered gene transcription

A number of large-scale genome-wide association studies have identified several genetic loci that harbor genes assumed to be associated with the development of SLE.^{21–24} However, none of the genes involved in the biochemical abnormalities described above (*CD44*, *CD247* and *FCER1G*) have appeared in these studies, a fact indicative of the complexity of the disease. Although polymorphisms in certain genes can predispose an individual to SLE, the presence of these polymorphisms does not always result in the phenotypic variations associated with disease. The immune system changes and adapts constantly, and the regulation of genes in lymphocytes is strongly influenced by environmental factors. The cell-signaling aberrations described above, combined with T-cell stimuli (such as anti-TCR–CD3 autoantibodies⁴ and circulating autoantigens), lead to altered gene expression that affects cell behavior and facilitates inflammation.

T cells integrate the stimuli they receive through the TCR and other receptors and produce a customized response in terms of cytokine production and expression of co-stimulatory molecules. Appropriate T-cell function relies on the transfer of external stimulation to the regulatory components of genes with fidelity, a process that is flawed in SLE T cells (Figure 1). thus, the regulation of expression levels and function of several transcription factors (proteins that bind to promoter regions of genes and control their expression) is altered in T cells from patients with SLE (Box 1).

NFAT

The NFAT (nuclear factor of activated T cells) family of transcription factors is regulated by intracellular calcium levels. TCR-mediated calcium influx causes dephosphorylation of inactive cytoplasmic NFAT and allows it to migrate into the nucleus, where it activates gene expression. levels of nuclear NFAT are abnormally increased in activated T cells from SLE patients,²⁵ which causes overexpression of CD40L, a co-stimulatory molecule that induces B-cell antibody production and dendritic cell activation.²⁶ The increased NFAT activity occurs without a corresponding increase in the levels of the transcription factor activator protein 1 (AP1). This unbalanced activation changes the effect of NFAT on a number of genes, and results in a complex alteration of gene transcription.⁵

CREB/CREM

The regulation of the cAMP-controlled transcription factors CREB (cAMP response element binding protein) and CREM is defective in T cells from patients with SLE.²⁷ although both bind to cAMP-responsive elements, their effects are antagonistic: phosphorylated CREB (pCREB) induces transcription, whereas CREM represses it. pCREB and CREM bind to the -180 site of the *IL2* promoter, and it seems that the ratio at which these two proteins bind this site determines the levels of IL-2 expression.²⁸ in SLE T cells, two exactly opposing mechanisms alter the ratio of these two proteins: increased levels of protein phosphatase 2 (PP2A), a serine/threonine phosphatase, cause dephosphorylation of pCREB,²⁹ whereas increased translocation of CAMK4 (calcium/calmodulin-dependent protein kinase IV) from the cytoplasm to the nucleus causes increased binding of CREM to DNA.⁴ levels of Fos, a component of the transcription factor AP1, are also low in SLE T cells owing to decreased CREB phosphorylation. ^{29,30} thus, decreased IL-2 production in SLE T cells results from an increased CREM:pCREB ratio and decreased AP1 activation.

DNA methylation

DNA methylation, which represents an important epigenetic mechanism involved in the suppression of gene expression, is decreased in T cells from SLE patients³¹ and results in overexpression of several proteins, including PP2A,³² CD7033 and CD40L.³⁴ Altered signaling, particularly via decreased mitogen-activated protein kinase (MAPK) activity,^{35,36} has been proposed to have a role, as this pathway regulates DNA methyltransferase activity. ³⁷⁻³⁹ Elevated levels of the proinflammatory cytokine IL-6 have also been shown to contribute to decreased DNA methylation in B cells from patients with SLE.⁴⁰

Box 1|Biochemical abnormalities in SLE T cells

Signaling molecules

- Decreased PKC activity
- Decreased PKA levels and activity
- Increased calcium response
- Decreased CD45 phosphatase activity

- Increased phosphorylation of tyrosine residues
- Decreased expression of CD3 ζ
- Decreased activity of Lck
- Increased expression of FcR γ
- Decreased MAPK activity
- Increased activity of PI3K
- Increased lipid raft clustering
- Increased expression and activity of Syk

Transcription factors

- Decreased NF κ B nuclear activity
- Increased binding of phosphorylated CREM to the IL-2 promoter
- Decreased binding of phosphorylated CREB to the IL-2 promoter
- Decreased nuclear translocation and DNA binding of AP1
- Decreased levels of functional Elf1
- Increased levels and nuclear translocation of NFATc2

Abbreviations: AP1, activator protein 1; CREB, cAMP response element binding protein; CREM, cAMP response element modulator; Elf1, E74-like factor 1; IL, interleukin; Lck, leukocyte-specific protein tyrosine kinase; MAPK, mitogen-activated protein kinase; NFATc2, nuclear factor of activated T cells, cytoplasmic 2; NF κ B, nuclear factor κ B; PI3K, phosphoinositide-3 kinase; PKA, protein kinase A; PKC, protein kinase C; SLE, systemic lupus erythematosus; Syk, spleen tyrosine kinase.

T cell subsets

According to the presence or absence of the coreceptors CD4 and CD8, TCR $\alpha\beta$ ⁺ T cells can be divided into CD4⁺, CD8⁺, and double negative (DN; CD4⁻CD8⁻) populations (Figure 3). CD4 and CD8 expression is determined in the thymus, whereas at least some of the DN T cells derive from a subset of activated CD8⁺ T cells.⁴¹

CD8⁺ and DN cells

The role of CD8⁺ T cells in SLE is not well determined. Patients with active SLE have increased numbers of activated CD8⁺ T cells,^{42,43} and CD8⁺ T cells are present in the kidneys of patients with lupus nephritis.⁴⁴ On the other hand, deficient CD8⁺ cytotoxic capacity has been reported in SLE.⁴⁵ In patients with the disease, the TCR $\alpha\beta$ ⁺ DN T cells are expanded,^{1,46} and may originate from CD8⁺ T cells that have lost surface CD8 molecules following stimulation with anti-CD3–TCR auto antibodies and autoantigens. 47–41 DN T cells infiltrate target organs (such as the kidneys),¹ produce proinflammatory cytokines (including IL-1 β and IL-17),^{1,48} and promote B-cell antibody production.^{49,50}

T_H17 cells

CD4⁺ T cells undergo functional differentiation after antigen priming, which grants them a distinct phenotype in terms of transcriptional regulation and cytokine production (Figure 3). Type 17 helper T (T_H17) cells are CD4⁺ T cells that express the transcription factors ROR γ t and ROR α and produce the cytokines IL-17A, IL-17F, IL-21, and IL-22.⁵¹ They induce intense inflammatory responses by secreting IL-17, which is a powerful neutrophil

attractant. Patients with SLE^{1,52} and lupus-prone mice^{53,54} have increased numbers of IL-17-producing T cells and elevated serum levels of IL-17.⁵⁵ Furthermore, IL-17-producing T cells have been observed among inflammatory infiltrates in kidneys affected by SLE.^{1,53,56,57} IL-17 can also stimulate B-cell antibody production,⁵⁵ and has been shown to participate in the formation of germinal centers in lupus-prone mice.⁵⁸

T_{FH} cells

Evidence indicates that follicular helper T cells (T_{FH}), a CD4⁺ subset, are involved in the pathogenesis of SLE. T_{FH} cells localize in germinal centers and stimulate B cells to produce antibodies and undergo somatic hyper-mutation and isotype switching through the expression of IL-21 and CD40L.⁵⁹ A subset of patients with SLE have increased numbers of circulating CD4⁺CXCR5⁺ cells, whose phenotype resembles T_{FH} cells (high expression of inducible T-cell costimulator [ICOS] and programmed death 1 [PD1]).⁶⁰ Likewise, in lupus-prone mice, disease development is accompanied by increased numbers of T_{FH} cells^{61,62} and extra-follicular T-helper cells (an analogous cell type found in extrafollicular germinal centers of autoimmune mice).⁶³ Moreover, the introduction of genetic deficiencies that halt the development of T_{FH} cells⁶² or extra-follicular T-helper cells⁶³ have a protective effect. Likewise, genetic deficiency of the IL-21 receptor rescues mice from lupus-like disease.⁶¹ IL-21 levels have also been reported to be abnormally high in patients with SLE.⁶⁴

T_{REG} cells

T_{REG} cells represent a constitutively suppressive CD4⁺ cell subset, characterized by the expression of the transcription factor FOXP3.⁶⁵ T_{REG} cells are necessary for the maintenance of immunological tolerance, and their absence causes a spontaneous and fatal autoimmune disorder.⁶⁵ T_{REG} cell numbers are low in patients with SLE,^{66–68} and their suppressive function is compromised.^{69,70} Some reports have highlighted the fact that SLE effector T cells may be particularly resistant to T_{REG}-induced suppression.⁷¹ In the context of SLE, T_{REG} cell deficiencies are probably related to the decreased production of IL-2,⁷² a cytokine that is essential for their development and survival,⁷³ and to elevated levels of proinflammatory cytokines, particularly IL-6,⁷⁴ which can inhibit T_{REG} cell function.⁷⁵ T_{REG} cell defects can contribute to SLE pathology by failing to control the response of other T cells and autoantibody production.⁷⁶ Patients with SLE who achieve remission have high levels of nonconventional T_{REG} cell populations.^{77,78} accordingly, therapeutic approaches to correcting IL-2 production or suppressing IL-6 levels seem worthy of consideration.

T-cell-targeted therapeutic approaches

Cell-based treatment

Autologous hemopoietic stem cell transplantation (HSCT) has been shown to induce long-term remission in patients with SLE refractory to standard therapies. In post-transplant patients, CD4⁺CD25^{high}FOXP3⁺ T cells, as well as an unusual subset of CD8⁺FOXP3⁺ T_{REG} cells, were shown to return to levels observed in normal individuals, accompanied by inhibited T-cell responses to histone peptides.⁷⁸ This clinical information, along with the report that infusion of natural T_{REG} cells in lupus-prone mice can suppress autoimmunity,⁷⁶ prompts further consideration of the potential of cell-based treatment in SLE.

Cognate cellular interactions

CTLA4–Ig (abatacept)—For optimal T-cell stimulation, the engagement of both the TCR and CD28 molecules with their receptors on the antigen-presenting cell is needed. Inhibition of the CD28–CD80/86 interaction would result in suboptimal activation of the T cell, despite adequate TCR engagement with the MHC–antigen complex. The activated T cell can

end its own stimulation by expressing CTLA4 (cytotoxic T-lymphocyte antigen 4; also known as CD152) on its surface. CTLA4 binds to CD80/86 with significantly higher affinity than CD28, thus out-competing the CD28 and preventing further T-cell activation. Abatacept (a CTLA4-Ig fusion molecule) was constructed with the aim of preventing the CD28-CD80/86 interaction. This agent was shown to be effective in improving disease activity in lupus-prone mice,⁷⁹ especially when given in combination with cyclophosphamide.⁸⁰ Abatacept combined with background mycophenolate mofetil treatment is currently being administered to patients with lupus nephritis in a phase II/III clinical trial. Another phase II trial of abatacept in patients already receiving cyclophosphamide and/or azathioprine for lupus nephritis is also under way.

CD40:CD40L—CD4⁺ and CD8⁺ T cells, as well as B cells, overexpress CD40L in patients with SLE.²⁶ Preclinical studies in lupus-prone mice with nephritis showed that treatment with an anti-CD40L antibody resulted in decreased disease severity and increased survival when compared to placebo-treated mice.^{81–83} Two different antibodies against human CD40L (BG9588 and IDEC-1) have been used in patients with SLE.⁸⁴ Treatment with BG9588,⁸⁵ but not IDEC-1,⁸⁶ resulted in improvement of serologic markers of disease activity (such as decreased anti-dsDNA titers, increased C3 concentration and decreased hematuria). Unexpectedly, anti-CD40L treatment resulted in thromboembolic events,⁸⁴ possibly through binding of the antibody to CD40L on the surface of activated platelets. As a result, clinical trials of these antibodies are currently in abeyance. The aberrantly increased expression of CD40L by SLE T cells might be abrogated by other pharmacologic agents that target the calcium influx and/or the phosphatase calcineurin;²⁵ these agents should not result in platelet aggregation and thrombotic events.

ICOS-B7RP1—Activated T cells express ICOS, which binds to B7-related peptide 1 (B7RP1; also known as inducible T-cell co-stimulator ligand [ICOSLG]). T cells use this pathway to induce class switching and IgG production by B cells. When an antibody against B7RP1 was injected into mice with lupus nephritis and inflammatory arthritis, it resulted in significant disease amelioration.^{87–89} One proposed mechanism for this observation is the inhibition of the development of T_{FH} cells, which help B cells in the germinal centers. A fully humanized anti-B7RP1 antibody (AMG557) is being evaluated in phase I trials in patients with SLE.

LFA1-ICAM1—LFA1 (lymphocyte function-associated antigen 1) expressed by activated T cells binds to ICAM-1 (intercellular adhesion molecule 1; also known as CD54) expressed on endothelial cells and stabilizes the immune synapse. The monoclonal humanized IgG1 antibody efalizumab, which targets the α -subunit of LFA1 (CD11a), has been used successfully in cases of severe cutaneous lupus erythematosus.⁹⁰ However, the association between efalizumab treatment and the development of progressive multifocal leukoencephalopathy in a number of patients led to its withdrawal from the market.

Cytokines

IL-6—Monocytes secrete IL-6,⁹¹ which, together with transforming growth factor β , promotes the differentiation of T_H17 cells. IL-6 levels are elevated in lupus-prone mice and in the serum and urine of patients with SLE, and can be detected in kidney biopsies of patients with lupus nephritis.^{92–95} Inhibition of IL-6 or IL-6 receptor (IL-6R) using specific antibodies resulted in clinical improvements in lupus-prone mice, including decreased anti-dsDNA antibody titers and proteinuria, and improved survival. The fully humanized monoclonal anti-IL6R antibody tocilizumab has shown promise in a phase I trial of SLE.⁹⁶ The treated patients had decreased levels of acute-phase reactants and small decreases in serum immunoglobulin and anti-dsDNA levels. However, as two patients developed severe

neutropenia, further studies are needed to address the efficacy and toxicity of this biologic agent in patients with SLE.

IL-17, IL-21 and IL-23—As discussed above, evidence stipulates the involvement of the cytokines IL-17, IL-21 and IL-23 in the development of SLE pathology both in mice and humans. Germline-targeted deletion of IL-21⁶¹ or IL-23 receptor resulted in significant mitigation of autoimmunity and glomerulo-nephritis, strongly supporting the consideration of these molecules as potential therapeutic targets in SLE.⁹⁷ An anti-CD3 antibody administered intranasally to lupus-prone SNF1 mice resulted in induction of CD4⁺CD25⁺LAP⁺ T_{REG} cells and suppression of IL-17⁺CD4⁺ICOS⁺CXCR5⁺ T_{FH} cells. As noted above, decreased T_{REG} cell function and increased numbers of T_{FH} cells have been implicated in the pathogenesis of SLE.⁹⁸ More information is needed to demonstrate the efficacy of anti-CD3 antibodies in other strains of lupus-prone mice, and whether the route of administration is important.

Signaling

Syk—Given the central role of Syk in the transduction of signals from various immune receptors and its involvement in SLE, an oral Syk inhibitor, fostamatinib (R788), was developed. Fostamatinib is a prodrug that is metabolized to the active compound R406. This drug was shown to be effective at reducing disease activity in a phase II trial of patients with rheumatoid arthritis,⁹⁹ and promising preclinical data have emerged from studies in lupus-prone mice and from *in vitro* studies of SLE T cells. R788 treatment of lupus-prone NZB/W F1¹⁰⁰ and MRL/*lpr* mice¹⁰¹ resulted in delayed disease onset and prolonged survival. Additionally, complementary work showed that R406 is able to block calcium influx in SLE T cells, thus correcting one of the major consequences of the altered TCR composition in SLE T cells.¹⁰

mTOR—Sirolimus (also known as rapamycin) is a lipophilic macrolide antibiotic that alters mitochondrial transmembrane potential and calcium fluxing, and is used primarily to control transplant rejection.¹⁰² Sirolimus binds FKBP1B and the regulatory kinase mTOR (mammalian target of rapamycin). This drug corrected some of the biochemical alterations of SLE T cells, including the decreased expression of CD3ζ.¹⁰³ Sirolimus was shown to prevent anti-dsDNA antibody production and glomerulonephritis and to prolong survival in lupus-prone mice.¹⁰⁴ Sirolimus also showed promising clinical results in nine patients with SLE.¹⁰⁵

CAMK4–CREM—Capitalizing on improvements of cellular transfection techniques, several key molecules in the abnormal signaling cascade in SLE T cells have emerged as potential therapeutic targets. CAMK4 has been shown to be a key molecule in the downregulation of IL-2 in activated SLE T cells. When T cells were transfected with a plasmid encoding a dominant-negative form of CAMK4,⁴ the enzymatic activity of CAMK4 was blocked and the production of IL-2 was boosted via inhibition of CREM binding to the *IL2* promoter.

T cells transfected with an antisense plasmid that suppressed production of CREM showed significantly increased production of IL-2²⁸ and c-Fos,³⁰ thus establishing the importance of the CAMK4–CREM pathway in the downregulation of IL-2 in SLE T cells. Gene therapy approaches that aim to suppress CREM and CAMK4 expression might be deserving of consideration as therapeutic approaches.

Adhesion

SLE T cells invade tissues via upregulation of surface adhesion molecules and rearrangement of their cytoskeleton. The enhanced adherence and migratory ability shown by SLE T cells is mediated by upregulated CD44. *In vitro* experiments have shown that silencing the expression of CD44 with specific small interfering RNA limits SLE T cells' ability to adhere and migrate.¹² The same outcome could be accomplished by blocking the phosphorylation of ERM (the intracellular signaling partners of CD44) by specific inhibition of Rho-kinase (ROCK), the kinase that activates ERM (Figure 2). Similarly, targeting the cytoskeletal rearrangement mechanism by blocking actin polymerization with cytochalasin D substantially impaired the ability of SLE T cells to adhere and migrate.¹⁰

Conclusions

T cells from patients with SLE display a fascinating phenotype that defies classification along the lines defined by the study of normal lymphocytes. Both at the cellular and cytokine level, SLE T cells present an antithetic signature. Although T cells can help B cells to produce autoantibodies at increased levels, they fail to generate cytotoxic and T_{REG} function. At the cytokine level, although they fail to produce IL-2, they release increased amounts of IL-6 and IL-17. Decreased levels of IL-2 may account for the suppressed cytotoxic responses and T_{REG} cell function and decreased elimination of autoreactive T cells through activation-induced cell death in patients with SLE. IL-17 is produced by several T-cell lineages, including CD4⁺ and CD3⁺CD4[−]CD8[−] T cells, which are expanded in SLE patients and are present in inflamed kidneys. CD44 seems to be expressed at increased levels on SLE T cells, and might account for their inappropriate tissue homing.

Advances in our understanding of the molecular workings of SLE T cells have begun to explain the SLE T-cell phenotype. Increased CD3–TCR-mediated calcium responses might, via increased NFAT levels, explain the increased expression of CD40L. Decreased production of IL-2 seems to be the result of increased CAMK4 expression, which causes increased binding of CREM to the IL-2 promoter, and increased PP2A expression, which leads to dephosphorylation of pCREB. The molecular cause of increased IL-17 production remains unknown. T-cell-targeted therapeutic approaches include blockade of T cell–B cell interactions, restoration of IL-2 and suppression of IL-17 production, and limiting the tissue-homing potential of T cells.

Identification of the unique biochemical abnormalities that seem to account for the aberrant T-cell function, such as increased Syk, CAMK4, and PP2A expression, calls for the development of small-molecule kinase/phosphatase inhibitors. Small-molecule inhibitors of Syk have been shown to suppress SLE pathology in animal models. Similarly, specific inhibitors of CaMK4 and PP2A may prove to have similar effects and deserve clinical testing. By virtue of restoring early and late T-cell signaling processes, these small-molecule drugs might correct effector T-cell function and prove of clinical value in patients with SLE.

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Figure 1.

Distinct biochemical abnormalities explain the unique phenotype of SLE T cells. Decreased levels of CD3 ζ and abnormal association of FcR γ with the CD3-TCR complex results in the 'rewiring' of the TCR through Syk rather than ZAP-70. The resulting increase in intracellular calcium concentration causes an imbalance in transcription factor activation, particularly toward high nuclear migration of NFAT. High CaMK4 activity, along with abnormally elevated PP2A levels, alters the balance between CREB and CREM in favor of the latter, leading to decreased transcription of IL-2. Abbreviations: CaMK4, calcium/calmodulin-dependent protein kinase IV; CREB, cAMP response element binding protein; CREM, cAMP response element modulator; IL, interleukin; NFAT, nuclear factor of activated T cells; PP2A, protein phosphatase 2; SLE, systemic lupus erythematosus; Syk, spleen tyrosine kinase; ZAP-70, ζ -chain-associated protein kinase 70.

Figure 2.

In vivo T-cell activation increases CD44 adhesion capacity and T-cell migration. T-cell stimulation by anti-CD3-TCR autoantibodies and/or autoantigens induces the activation of ROCK. ROCK phosphorylates ERM proteins, which then associate with CD44. The net effect is an increase in the adhesion and migration capacity of the T cell. Abbreviations: ERM proteins, ezrin, radixin and moesin proteins; ROCK, Rho kinase; TCR, T cell receptor.

Figure 3.

Differentiation of T-cell subsets is biased in patients with SLE. Increased production of IL-6 by APCs, along with decreased IL-2 secretion by T cells, facilitates the differentiation of IL-17-producing cells whilst inhibiting the development of T_{REG} cells. T_{FH} cells, a CD4 subset specialized in providing help to B cells via expression of CD40L and IL-21 is also enhanced in SLE. These cells, along with elevated mononuclear IL-10 production, stimulate B cells to produce autoantibodies. Generation of proinflammatory DN (CD4⁻CD8⁻) T cells from CD8⁺ precursors is increased in patients with SLE, and CD8⁺ cytotoxic T-cell responses are diminished. Abbreviations: APC, antigen-presenting cell; CD40L, CD40

ligand; DN, double negative; IL, interleukin; SLE, systemic lupus erythematosus; T_{FH} cell, follicular helper T cell; T_H17 cell, type 17 helper T cell; T_{REG} cell, regulatory T cell.