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T cells in Systemic Lupus Erythematosus

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Abstract

Systemic Lupus Erythematosus is an autoimmune disorder caused by a complex combination of genetic, epigenetic and environmental factors. Different polymorphisms and epigenetic modifications lead to altered gene expression and function of several molecules which lead to abnormal T cell responses. Metabolic and functional alterations result in peripheral tolerance failures and biased differentiation of T cells into pro-inflammatory and B cell-helper phenotypes as well as the accumulation of disease-promoting memory T cells. Understanding these T cell alterations and their origins is necessary to develop more accurate patient classification systems and to discover new therapeutic targets.

Graphical Abstract

Introduction

SLE is a complex autoimmune disease characterized by defects in cellular apoptotic debris clearance, an interferon (IFN) expression signature in peripheral lymphocytes, and the breakdown of peripheral tolerance mechanisms resulting in the generation of autoantibodies and damage of tissues and organs, including the kidney (reviewed in [1]). T cells play a major role in SLE pathogenesis, amplifying inflammation by secretion of pro-inflammatory cytokines, helping B cells to generate autoantibodies, and maintaining the disease through

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the accumulation of autoreactive memory T cells. Many aberrations in T cell expression and function have been described as related to abnormal T cell activation in SLE patients (reviewed in [2]) which leads to reduced TCR activation threshold and reduced peripheral tolerance.

During the last few years, special interest has been focused on the role of T cell subsets in SLE pathology, the molecular pathways involved in their aberrant differentiation and their varied metabolic needs. In this review we discuss the role of T cells in SLE as well as current knowledge of associated molecular alterations. Clearer understanding of these aberrations will lead to the development of new and more specific SLE treatments.

SLE T cells show widespread inflammatory gene expression

In addition to the IFN gene signature, T cell transcriptome data highlights induction of pathways related to mitochondria, glycolysis and nucleotide metabolism, as well as genes induced in patients with anti-dsDNA antibodies and nephritis. T cell gene expression can also be used to stratify patients into subtypes which may facilitate precision medicine approaches [3]. Many of the induced genes are present in other peripheral blood cells ([4]). While some of the altered genes and pathways are already validated in the literature, such as increased mitochondrial oxidative phosphorylation and glycolysis [5], further validation and functional analysis should lead to a better understanding of the disease and development of new and more precise (personalized) therapeutic treatments.

T cells, a complex group of different cells with specific functions that are altered in SLE

Recent advances in detection methods reveal immense complexity in peripheral blood T cell subpopulations [6], including different effector, memory and regulatory subtypes.

While the immune system relies on complex interactions of different cells, these can be broadly classified as pro- or anti-inflammatory. T cells can drive immunosuppression or inflammation and antibody production, based on the proportion of different T cell subpopulations and their signaling function. The prevalence of T cell subtypes can vary widely but SLE patients show consistent differences in the ratios of some T cell subsets as well as abnormalities in their function (Fig. 1). The role of these cells in SLE pathogenesis has been studied during the last years and are commented on below.

Reduced cytotoxicity in SLE CD8 T cells

CD8 T cells control infection, malignancy and autoreactive immunity by release of cytotoxic proteins such as perforin and granzymes. CD8 T cells in SLE have dampened cytotoxic function that can lead to increased risk of infection, which may also trigger autoimmunity [7]. Two recent studies showed defective CD8 responses to viral antigens, and proposed either a reduction in effector memory CD8 T cells positive for Signaling lymphocytic activation molecule family member 4 (SLAMF4) which is related to conversion of CD8 into double negative (DN) T cells [8], or increased expression of the inhibitory programmed

death receptor 1 (PD-1) [9], an inhibitory receptor that is expressed under continuous TCR stimulation without co-stimulatory molecules. Induction of exhaustion has been proposed as therapy for autoimmune disease, as an exhaustion transcriptome profile marks patients with better clinical outcomes [10]. Such therapies may increase susceptibility to infections, the highest cause of death in SLE, so careful consideration will be required [1]. In addition, PD-1 plays a role in the generation of DN T cells from autoreactive T cells [11], which plays a pathogenic role in SLE. The conversion of CD8 T cells into double-negative T cells, as well as PD-1 expression, could explain the loss of cytotoxicity against viruses in SLE CD8 T cells.

Double-Negative T cells in SLE: from suppressive to pro-inflammatory

Double-Negative (DN) T cells, defined as $\text{TCR}\alpha\beta^+\text{CD4}^-\text{CD8}^-$, can result from inactivation or exhaustion of autoreactive, or continuously stimulated CD8 T cells, such as are found in chronic infection [12,13]. Under normal conditions an immunosuppressive role has been attributed to these cells, both in mouse and human, through antigen-competition and T cell killing by Fas-FasL or perforin and granzyme secretion [14,15]. However, in SLE patients these cells are related to pathogenesis and kidney disease where they accumulate and produce the pro-inflammatory cytokine IL-17 [16] (Fig. 1).

Increased mitochondrial mass and mitochondrial potential dysfunction have been described in DN T cells from SLE patients, leading to mTOR activation and expansion of DN T cells producing IL-17 [17]. Increased expression and activation of CREM α in SLE T cells was also shown to contribute to generation of DN T cells [18] and IL-17 production [19]. Additionally, the immunosuppressive function of DN T cells is affected by PI3K/AKT/mTOR activity [20], which is increased in SLE T and B cells [21](Fig. 2).

CD4 T helper cells, supporting inflammation and autoantibody production in SLE

CD4⁺ helper T cells make major contributions to antibody production and tissue inflammation, and are readily linked to development of SLE and Lupus nephritis. Aberrant expression of different molecules and signaling leads to increased TCR stimulation and circumvention of peripheral tolerance mechanisms (Fig. 2 and [2]). In addition, increased accumulation of effector/memory T cells has been described in these patients, which is thought to result from activation of PI3K/AKT/mTOR transduction, conferring resistance to activation-induced cell death [21]. In addition to effector/memory T cell accumulation, there is a skewing toward T Helper (T_H)17 cell production with down-regulation of the T_H1 and regulatory T cell (T_{reg}) cytokines, IFN γ and TGF β , and the up-regulation of IL-6 and IL-17, T_H17 cytokines [22]. Additionally, an increase in a subpopulation of extra-follicular T helper cells has been described in peripheral blood from SLE patients, helping to explain increased B cell activation and autoantibody production [23–26].

Increased numbers of T helper 17 cells promote kidney disease and autoantibody production

T_H17 cells and the cytokine IL-17 are related to SLE disease and especially with lupus nephritis (Fig. 1). IL-17 is a potent pro-inflammatory cytokine, the levels of which correlate with the development of lupus-like nephritis in several mouse models. In addition, the proportion of T_H17 cells and the amount of IL-17 in serum are increased in SLE patients, especially in those with kidney disease (Fig. 1 and reviewed in [27]).

There are several molecular aberrations in SLE patients that lead to an increase in IL-17 production and TH-17 kidney infiltration (Fig. 2). Stimulation of SLE T cells through TLR2, a molecule increased in SLE CD4 T cells upon activation of the Syk pathway [28], leads to chromatin opening at the promoters of IL-17A and IL-17F through increased histone acetylation and reduced DNA methylation [29], and activates NF- κ B [30]. The protein phosphatase (PP) 2A is increased in SLE T cells; it also controls the IL-17 promoter, inducing hypomethylation by suppressing the DNA methyltransferase 1 pathway, promoting acetylation of histone 3 [31,32], and facilitating the binding of IRF4 which is activated by Rho-associated protein kinase (ROCK)[33]. Activation of CaMKIV leads to CREM α and ROR γ binding to the IL-17 promoter and the transcription of this cytokine via activation of the PI3K/AKT/mTOR pathway [19]. In addition, CAMKIV has been linked to expression of CCR6, which facilitates recruitment of T_H17 cells to the kidney[34]. AKT inhibition reduces in vitro T_H17 migration in response to CCL-20 [35], probably as a consequence of altered signaling through ROCK, which is more active in SLE T cells and is involved in CCR6 and CD44 signaling [36]. IL-17 also contributes to the loss of B cell tolerance in an autoimmune mouse [37], adding a new role to DN and T_H17 cell function in SLE pathogenesis.

Extrafollicular T cells help B cells to produce autoantibodies in SLE

SLE is characterized by production of high affinity autoantibodies against nuclear antigens, of which anti-dsDNA has been most correlated with disease activity[1]. The IgG isotype and somatic hypermutation in these autoantibodies indicates that that B cells are activated in a T-cell dependent-manner [38]. B cell activation depends on interaction with T follicular helper (T_{FH}) cells, a subtype of CD4 T cells positive for CXCR5, PD-1, ICOS and CD40L. In addition these cells express high levels of IL-21 and IL-10 which costimulate B cells to differentiate into memory B cells and plasmablasts [39].

Several groups have shown significant increases in T cells with a follicular helper-like phenotype in peripheral blood from SLE patients [23–26]. These cells are characterized by CXCR5 expression. These cells also express ICOS, PD-1, CD57, BTLA, and produce IL-21, confirming the T_{FH}-like nature of these cells [24,26].

The number of extrafollicular T helper cells correlates with antibody titers, especially anti-DNA and plasmablast B cells in peripheral blood from SLE patients. In addition these cells have been found in lymphoid aggregates and ectopic germinal centers in lupus nephritis lesions expressing ICOS, PD-1, Bcl-6 and IL-21 [40]. Induction of B cell differentiation into

plasmablasts depends on CD40L but not on ICOS expression in T_{FH} [25]. However, ICOS signaling, as well as OX40, through p110δ, are necessary for T_{FH} differentiation [41,42].

T_{FH} differentiation requires Bcl-6, a transcription factor regulated by Signal transducer and activator of transcription (STAT)3, following IL-6 and IL-21 stimulation which can be inhibited by IL-2 through STAT5 activation [43–45]. The combination of signals that are necessary needs further investigation since contradictory data exists on the role of the PI3K/AKT/mTOR pathway [46,47]. Down-regulation of IL-2, increased levels of IL-6 and IL-21 in serum from SLE patients [48], and higher expression of ICOS and OX40 on SLE T cells can lead to increased differentiation of T_{FH} over T_{H1} cells and support autoantibody production both in classical and ectopic germinal centers (Fig. 1 and 2).

γδT cells

γδT are a minor population of T cells related to SLE pathology, both in humans and in mouse models, through their antigen-presenting function, pro-inflammatory cytokine secretion, interaction with T_{reg}, and their promotion of antibody production by providing B cell help even in absence of antigen (reviewed in [49])

Recently, a report showed that one subtype of the γδT cell population, Vδ2, is reduced in peripheral blood but accumulates in kidneys from SLE patients. These cells display an activated phenotype with expression of different chemokine receptors, CD40L and IL-21, indicating a possible role in B cell stimulation [50] and a role for γδT cells in lupus nephritis.

Impaired Regulatory T cells in SLE

T regulatory cells (T_{reg}) include several subsets of T cells playing a critical role in the control of the immune system. While the classical T_{reg} are a subset of the TCRαβ CD4⁺ cells, TCRαβ CD8⁺ and γδT cells have also been described to have regulatory activity (reviewed in [51]). While it is well accepted that there is a dysregulation in immune response control by T_{reg} in SLE patients, the cause remains unclear.

CD4⁺ T Regulatory Cells

CD4 T_{reg} cells are marked by high expression of IL-2 receptor alpha (CD25) and transcription factor Forkhead box P3 (FoxP3), coupled with low levels of IL-7 receptor alpha (CD127). Because different markers are used in the literature, the number of T_{reg} in the peripheral blood of SLE patients, as well as their function are conflicting (reviewed in [52]). A dysregulation between effector and T_{reg} balance is evident and this may be a result of several molecular aberrations. Activation of the PI3K/AKT/mTOR [21,53] and CaMKIV [54] pathways in SLE T cells accounts for differentiation into T_{H17} or DN negative T cells and reduced differentiation into T_{reg} by a mechanism that implicates IL-2 shortage [19,53]. This is supported by recent studies in lupus-prone mice where inhibition of CaMKIV, which restores IL-2 production [55], or increased IL-2 production by gene-therapy [56], enhanced T_{reg} levels resulting in diminished organ inflammation. Even more compelling, clinical trials showed that low doses of IL-2 reduced disease activity, coupled with expansion of the T_{reg}

cells and decreased levels of anti-dsDNA antibodies in SLE patients [57,58]. Rapamycin treatment of SLE T cells *in vitro* leads to expansion of T_{reg} with sustained suppressive activity [53,59], and a clinical trial using N-acetylcysteine, an inhibitor of mTOR, also showed reduced disease activity and increased T_{reg} populations [60].

CD8+ T Regulatory Cells

CD8 T regulatory cells (CD8 T_{reg}) also express FOXP3, high levels of CD25 and low levels of CD127, but also several membrane molecules such as CTLA-4, GITR, etc., (reviewed in [61]). CD8 T_{reg} inhibit immune responses through mechanisms such as cytokine release or direct contact with target cells. Importantly, it has been shown that CD8 T_{reg} control adaptive immune responses through inhibition of follicular helper T cells mediated by Qa-1, the ortholog of human HLA-E [62]. CD8+ T_{reg} from patients with SLE show defective suppression of effector T cell proliferation [63,64]; however, more studies are required to further characterize specific functions of these cells in SLE patients. Interestingly, antibodies against HLA-E have been described in SLE serum [65], raising the possibility that these antibodies are interfering with CD8 T_{reg} activity.

γδ Regulatory T Cells

A subpopulation of γδT cells expressing FoxP3, high levels of CD25 and CD27, and low levels of CD45RA, also can suppress autologous T cell proliferation. SLE patients showed significantly fewer circulating γδT_{reg} cells in the periphery [66], but more studies are needed in order to define the function of these cells.

Conclusions

T cells play an important role driving and maintaining SLE disease. Decreased cytotoxicity of CD8 T cells has a role in increased risk of infection. Up-regulation and accumulation of T follicular helper, γδT cells, T_{H17} and DN T cells, and down-regulation of suppressive function of the different regulatory subsets, drive and maintain the synthesis of autoantibodies and have a strong influence over kidney pathology in SLE patients (Fig. 1). At the molecular level, the pathways and molecular aberrations that lead to activation of CaMKIV, ROCK, STAT3 and PI3K/AKT/mTOR are important for differentiation of T_{H17} and T_{FH} and for suppression of differentiation and function of Treg. These molecules seem to be promising therapeutic targets with clinical trials underway (Fig. 2). Careful consideration of T cell subsets, coupled with patient stratification by immunophenotyping and expression analysis, holds great promise for the development of new and more personalized therapies in SLE.

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Highlights

- T cell transcriptomes can stratify patients.
- T_H17, Double Negative and $\gamma\delta$ T cells contribute to lupus nephritis.
- T cell support autoantibody production in lymphoid and non-lymphoid organs in SLE.
- Aberrant activation of several pathways drives T cell malfunction in SLE.
- CaMKIV, ROCK, STAT3 AND PI3K/AKT/mTOR represent therapeutic targets.

Figure 1. Dysregulation of T cell function and subpopulation ratios drive SLE pathogenesis
 Reduced T cell regulatory and cytotoxic functions lead to increased pro-inflammatory and follicular helper T cell subpopulations that infiltrate tissues contributing to inflammation and auto-antibody production (red line indicates up-regulated and the blue line for down-regulated).

Figure 2. Aberrant signaling in SLE T cells leads to impaired regulatory function and differentiation into TH17 and TFH cells

The different pathway colors are arbitrarily assigned to facilitate visualization.