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T Cells as Treatment Targets in Systemic Lupus Erythematosus

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Abstract

T cells play a central role in Systemic Lupus Erythematosus (SLE) pathogenesis. The discovery of key steps that lead to SLE T cell dysfunction allowed several investigators to propose targeted treatments for SLE. Herein, we discuss the potential of novel drugs targeting SLE T cells, such as fostamatinib and anti-IL-17 antibodies. Furthermore, we discuss the use of already approved medications such as rapamycin, dipyridamole and N acetylcysteine as targeted therapies for SLE.

Keywords: T cells; Systemic lupus erythematosus; Therapy; Calcium; Interleukins

Introduction

Although the cause of systemic lupus erythematosus (SLE) is unknown, intensive investigation into the nature of the autoimmune response that underlies SLE, has revealed several key signaling aberrations that can be exploited therapeutically (summarized in Figure 1). For example, the cytokine B lymphocyte stimulator (BLyS), shown to be increased in SLE, was targeted with a monoclonal antibody resulting in a modest yet significant improvement in SLE disease activity [1]. Despite these advances, the treatment of SLE patients is still based on non-specific immunosuppressants that have significant off-target effects.

The Nature of T cell Response in SLE

The abnormal immune response in SLE is in large part driven by a misguided T cell. More precisely, SLE T cells fail to appropriately regulate (suppress) the immune responses, provide excessive help to B cells to produce autoantibodies and invade tissues such as the kidneys, causing in situ damage. What became apparent early on in the study of SLE T cells is that they respond to T Cell Receptor (TCR) stimuli in a unique way. Pivotal cytokines such as interleukin (IL)-2 are not produced at high enough levels while co-stimulatory molecules such as CD154 (CD40ligand, CD40L) that provide help to B cells show high and sustained expression [2].

Part of the answer for this aberrant SLE T cell behavior lies in the structure of the TCR itself and its distribution on the surface of SLE T cells. The TCR heterodimer associates with the CD3 complex that transduces inward the signal created when the TCR binds to its cognate antigen. In SLE T cells, the canonical CD3ζ chain, the main signal transducing molecule in the CD3 complex, is decreased and in part substituted by the FcRγ chain. This CD3ζ to FcRγ substitution leads to the recruitment of the spleen tyrosine kinase (Syk) to the TCR/CD3 complex. Syk in turn leads to excessive calcium flux in the T cell, which causes hyper-stimulation of the T cell.

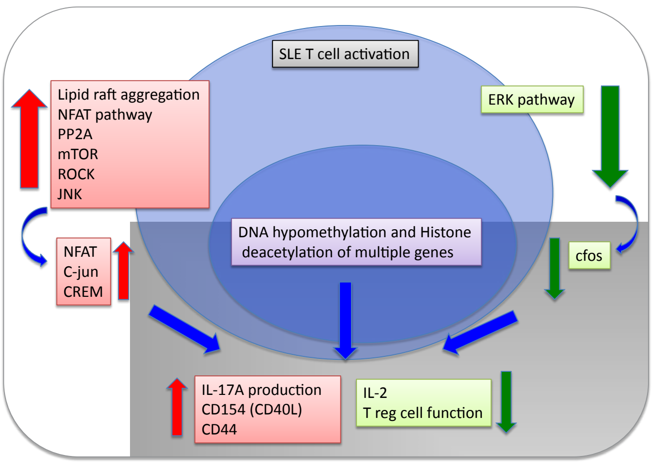

Figure 1: Signaling aberrations in Systemic Lupus Erythematosus T cells.

The activation of SLE T cells is further enhanced by the alignment of the TCR in lipid rafts. The lipid rafts are cholesterol rich areas of the T cell membrane that help bring together the surface signaling molecules. In SLE T cells unlike healthy individual T cells, lipid rafts are aggregated in one pole of the cell further facilitating SLE T cell activation. Furthermore, decrease in glutathione and excessive oxidative stress lead to mitochondrial hyperpolarization in SLE T cells, in turn contributing to activation of the mammalian target of rapamycin (mTOR) pathway, a regulator of post activation cell fate.

The effect of these proximal events in SLE T cell signaling together with other yet unrecognized factors is the imbalanced activation of cytoplasmic enzymes, mainly kinases and phosphatases. Activated SLE T cells show high activity of the calcineurin-nuclear factor of activated T cells (NFAT) pathway, protein phosphatase (PP)2A, mTOR, rho kinase (ROCK), Calcium/Calmodulin kinase IV(CaMKIV) and c-jun N-terminal kinase (JNK) pathways, while the ERK pathway is down-regulated. These changes in the cytoplasmic signaling cascades lead to excessive nuclear recruitment of the transcription factors NFAT, c-jun, and c-AMP response element modulator (CREM) and the decreased expression of the transcription factor c-fos in the nucleus of the cells. Furthermore they facilitate the de-acetylation of histones and hypomethylation of DNA in SLE T cells. Imbalanced transcription factor recruitment on gene promoters, histone deacetylation and hypomethylation of these promoters are the hallmark of SLE T cell activation. The end result is the production of certain proinflammatory cytokines such as IL-17A. Moreover, these signaling events lead to the increased and sustained expression of surface molecules such as CD154 that provides help to B cells and CD44 that enables cell adhesion and

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migration. Finally deficient IL-2 as well as increased mTOR activity are contributing to deficient T regulatory cell function.

SLE T Cells as Therapeutic Targets

One of the most obvious targets for therapeutic intervention is the rewired TCR receptor in SLE T cells. Moulton et al. [3] identified the splicing protein alternative splicing factor/splicing factor 2(ASF/SF2) as regulator of the CD3ζ chain expression in human T cells. ASF/SF2 increases the levels of CD3ζ chain mRNA by limiting the expression of the alternatively spliced unstable mRNA isoform. More importantly, forced expression of ASF/SF2 results in normalization of the CD3ζ levels and subsequent restoration of IL-2 production in vitro by SLE T cells [3].

T cell hyperactivity can also be suppressed by targeting the kinase Syk. Syk can be blocked by the small molecule fostamatinib (also called R788), which is in late stage development for the treatment of rheumatoid arthritis [4]. R406 (the active metabolite of R788) was shown to normalize the hyperactive phenotype of SLE T cells in vitro without having an effect on healthy donor T cells. When given in mice, R788 prevented the development of nephritis and dermatitis and even had an effect in mice with established nephritis [5].

The oxidative stress and subsequent mTOR activation in SLE T cells was addressed in two studies. In the first open label study, rapamycin, that binds mTOR, was found to be effective in decreasing disease activity as measured by SLE disease activity index (SLEDAI) and corticosteroid use [6]. Importantly the treatment with rapamycin resulted in decreased calcium flux by SLE T cells. N-Acetyl Cysteine (NAC) which repletes glutathione and thus reverses mitochondrial hyper polarization, was also shown by the same group to have a modest effect on SLE disease activity in a large placebo controlled trial [7].

As discussed earlier the hyperactivated SLE T cell acts as a potent helper to B cells for the production of high affinity pathogenic autoantibodies in SLE. This interaction is facilitated by increased and prolonged expression of CD154 on SLE T cells. Direct inhibition of this molecule with a monoclonal antibody decreased production of dsDNA and increased C3 levels; moreover hematuria disappeared in all (5/18) patients who had hematuria at baseline. Nevertheless the study was prematurely stopped due to excessive thromboembolic events [8]. This may have been due to off-target effects of the antibody on platelets and hence a strategy to inhibit CD154 production in T cells is more attractive than direct non-specific inhibition with antibodies. CD154 expression is dependent on the calcineurin-NFAT pathway and hence amenable to inhibition by calcineurin inhibitors. In a recent study, dipyridamole, recently recognized as a calcineurin-NFAT inhibitor, blocked the expression of CD154 by T cells, prevented the development of dermatitis and alleviated nephritis in lupus prone mice [9]. Dipyridamole, a drug with a long track record and favorable side-effect profile when compared to traditional calcineurin inhibitors cyclosporin and tacrolimus, represents therefore a potentially novel treatment for SLE patients.

The abnormal SLE T cell activation can also be corrected by directly altering the methylation of DNA and acetylation of histones, two of the most important epigenetic factors used by T cells to activate their genes. The histone deacetylase (HDAC) inhibitor trichostatin A has been found to reverse the abnormal SLE T cell signaling phenotype including the expression of CD154, and intereferon gamma [10]. Trichostatin ameliorated disease in lupus prone mice [11], suggesting that it may be effective in patients with SLE. The HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) was also shown also to ameliorate disease in MRL/lpr cells without affecting autoantibody production [12]. SAHA or vorinostat is currently being used as a treatment for cutaneous T cell lymphoma.

SLE T cells besides helping B cells, produce various pro-inflammatory cytokines. Of particular importance is the observation that SLE T cells in the peripheral blood and kidneys of patients with nephritis are IL-17 producers. IL-17 is an important pro-inflammatory cytokine that is being targeted in a variety of autoimmune diseases. Using lupus prone mice, it was shown that IL-17 production can be decreased in the absence of the receptor for the IL-23. Indeed, IL-23 receptor deficient lupus prone mice were completely protected from development of lupus [13]. These preclinical experiments suggest that SLE is a good target for the emerging IL-17 and IL-23 targeting therapies [10].

SLE T cells orchestrate the inflammatory response in target tissues such as the kidney. The process of migration of SLE T cells into these organs is facilitated by the enhanced expression of CD44 and its association with the phosphorylated of Ezrin Radixin and Moesin (ERM). Inhibition of ERM phosphorylation by rho kinase (ROCK) inhibitors resulted in a significant impairment of SLE T cell migration in vitro [14]. Interestingly ROCK plays an important role in the development of Th17 cells in both mice and humans [15, 16] and its activity is increased in a subset of patients with SLE [16]. Therefore targeting ROCK may decrease T cell migration to the kidneys and local production of inflammatory cytokines. Indeed the ROCK inhibitor

Target	Modality	Effect
TCR	ASF/SF2 forced expression	Increase in IL-2 production in vitro
Syk	Fostamatinib	Normalization of calcium flux in vitro Amelioration of disease in lupus prone mice
mTOR	1. Rapamycin 2. N-Acetyl cysteine	1. Improvement of SLE disease activity in patients and decrease in corticosteroid use 2. Improvement of SLE disease activity in patients
CD 154	1. Anti-CD154 antibodies 2. Tacrolimus/Cyclosporine 3. Dipyridamole	1. Improvement of serological activity and hematuria. Trials stopped due to myocardial infarctions. 2. Used in patients with lupus nephritis 3. Ameliorated disease in lupus prone mice
HDAC	1. Trichostatin A 2. Vorinostat	Decrease expression of interferon gamma in vitro Amelioration of disease activity in lupus prone mice
IL-23	IL-23 receptor deficiency	Amelioration of immune activation and nephritis in IL-23 receptor deficient animals
ROCK	Fasudil	Amelioration of disease in lupus prone mice
CaMKIV	KN93	Increase in IL-2 production in vitro Amelioration of disease through inhibition of Interferon gamma in lupus prone mice
Treg	1. IL-2 infusion 2. Treg cell therapy	1. Effective in graft versus host patients 2. Amelioration of disease in lupus prone mice

Table 1: N-acetyl cysteine and dipyridamole together with anti-IL17/IL-23 monoclonal antibodies show significant promise as T cell targeting SLE therapies.

fasudil ameliorated nephritis in lupus prone mice [17], opening the way for human trials.

In addition to the aforementioned mechanisms, SLE T cells fail to appropriately regulate the immune response appropriately, partly due to decreased production of the Treg trophic cytokine interleukin-2. Several mechanisms have been shown to cause IL-2 deficient production by SLE T cells. One of the most prominent is the upregulation of CaMKIV that recruits the transcription repressor CREM to the IL-2 promoter [18]. Indeed, the small molecule inhibitor of CaMKIV, KN-93 was shown to be effective in ameliorating disease in lupus prone mice [19]; KN-93's main effect though was inhibition of interferon gamma production suggesting that CaMKIV may be important for multiple pathogenic pathways in SLE.

In a very important study in patients with graft versus host disease, low dose IL-2 may boost preferentially Treg function without causing widespread immune activation [20]. Therefore, reconstituting IL-2 production by T cells or exogenous IL-2 infusion hold promise to improve Treg function in SLE as well. A more ambitious approach would be to isolate and expand Treg in vitro and re-infuse them in SLE patients. Indeed, this has been shown to be feasible and effective in lupus prone mice [21] opening the way for cell based therapy in SLE.

Conclusion

New molecules like fostamatinib and established medications like rapamycin, N-acetyl cysteine and dipyridamole together with anti-IL17/IL-23 monoclonal antibodies show significant promise as T cell targeting SLE therapies (summarized in Table 1). Large placebo-controlled studies will be needed to establish their usefulness and their exact place in the treatment regimens for SLE.

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