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Genes, Tolerance and Systemic Autoimmunity

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Abstract

The characterization of functional CD8⁺ inhibitory or regulatory T cells and their gene regulation remains a critical challenge in the field of tolerance and autoimmunity. Investigating the genes induced in regulatory cells and the regulatory networks and pathways that underlie mechanisms of immune resistance and prevent apoptosis in the CD8⁺ T cell compartment are crucial to understanding tolerance mechanisms in systemic autoimmunity. Little is currently known about the genetic control that governs the ability of CD8⁺ T_H1 or regulatory cells to suppress anti-DNA Ab production in B cells. Silencing genes with siRNA or shRNA and overexpression of genes with lentiviral cDNA transduction are established approaches to identifying and understanding the function of candidate genes in tolerance and immunity. Elucidation of interactions between genes and proteins, and their synergistic effects in establishing cell-cell cross talk, including receptor modulation/antagonism, are essential for delineating the roles of these cells. In this review, we will examine recent reports which describe the modulation of cells from lupus prone mice or lupus patients to confer anti-inflammatory and protective gene expression and novel associated phenotypes. We will highlight recent findings on the role of selected genes induced by peptide tolerance in CD8⁺ T_H1.

Keywords

Autoimmunity; Systemic Lupus Erythematosus; CD8⁺ Treg; Genes and Tolerance

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by widespread inflammation, autoantibody production, and immune complex deposition. While SLE affects multiple major organ systems in the body, lupus nephritis is the leading cause of death. Approximately two million people suffer from SLE with the majority of cases being women of childbearing age. Lupus is a gender-biased disease with a female to male ratio of 9:1. African American women are three times more likely to get lupus (SLE) than white women. Lupus is also more common in Hispanic, Asian, and Native American women. In SLE, immune homeostasis is impaired, and both T and B cells acquire abnormal characteristics in terms of activation, cytokine production, and proliferative potential. The modulation of abnormal immune regulation is the subject of intense investigations in several experimental

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autoimmune diseases. Significant therapeutic goals include limiting the number of abnormal pathogenic cells and autoantibodies, and restoration of immune system self-tolerance by the administration of peptides that induce regulatory/inhibitory T cells (Ti).

Decreased numbers, and or impaired function, of CD4⁺ regulatory T cells (Treg) have emerged as an important pathogenic mechanism in SLE [1–9]. Targeting of regulatory CD4⁺ T cells and CD8⁺Ti in SLE for therapeutic purposes through use of self-peptides to alter the functional properties of these cells and to halt disease progression has been attempted [10–19]. We have shown previously that BWF1 lupus mice are protected from autoimmune disease after *i.v.* injection of high doses of pConsensus (pCons), a synthetic peptide based on sequences of murine anti-dsDNA antibodies that are presented by both MHC class I and II molecules [11]. Tolerance induction by pCons peptide treatment enhances the numbers of both CD8⁺Ti and CD4⁺ Treg. Critically, both of these cell populations suppress the proliferation of effector CD4⁺CD25[–] CD4⁺ T cells and B cells [8, 10, 16, 17, 19]. We also have evidence that pCons peptide induces Treg in SLE patient cells *in vitro* and these cells suppress the proliferation of autologous CD4⁺CD25[–] effector cells. Furthermore, we found an inverse correlation between the expression levels of the *Foxp3* gene in Treg and SLE disease activity (SLEDAI) [20]. In this review, we will discuss some of our recent findings and highlight the work of others in the field.

2. Potential contributions of CD8⁺ regulatory T cells to immune tolerance in Lupus

The role of CD8⁺ Ti as Treg has only recently begun to be examined as a novel approach in the field of immune tolerance [21–24]. Clues to the regulatory function of CD8⁺T cells have emerged from studies in autoimmune diseases such as experimental autoimmune encephalomyelitis [25–28], myasthenia gravis [29], and SLE [21, 30–33]. Recent studies have provided evidence that both CD4⁺ Treg and CD8⁺ suppressor T cells play crucial roles in the prevention of autoimmunity [6, 8, 10, 16, 17, 34–36]. Via and colleagues recently ascribed to donor CD8⁺T cells a role in the prevention of lupus in a murine model of graft vs host disease, by inhibition of effector T cells that cause the disease [37–39]. Fan and Singh reported that therapeutically induced CD8⁺CTL kill autoantibody-producing B cells and inhibit murine lupus [40]. By administration of nucleosomal histone peptides to (SWRXNZB) F1 (SNF1) mice, Datta and colleagues induced CD4⁺ and CD8⁺ TGFβ⁺ Treg that subsequently delayed B cell activation and nephritis [13, 41]. This group also reported that TGFβ⁺-producing human CD8⁺ Treg are associated with immunological remission of lupus following autologous hematopoietic stem cell transplantation in SLE patients [32]. Kumar and colleagues showed that Qa-1 restricted CD8αα⁺ TCRαβ⁺ T cells regulate immunity [23, 42, 43]. Using the BWF1 SLE mouse model, Mozes' group studied induced Treg in mice treated with a tolerogenic peptide based on the light chain complementarity-determining region 1 (hCDR1) of human anti-dsDNA antibodies [15, 44]. Tolerization of mice with hCDR1 induced CD4⁺CD25^{high} and CD8⁺CD28 Treg, which suppressed lymphocyte proliferation and autoantibody production [45]. We found, in our similar model of tolerance induced by pCons, that inhibitory cells were present in both CD8⁺CD28⁺ and CD8⁺CD28[–] subsets. However, the expression of *Foxp3* and TGFβ mRNAs was higher and lasted longer in the CD28[–] subsets [17]. Recently, the Cantor group described a population of Qa-1 restricted CD8⁺ T cells that inhibit lupus-like disease and target autoreactive CD4⁺T follicular helper cells (T_{FH}) [22, 46]. These CD8⁺ Ti cells maintain self-tolerance by recognition of Qa-1 peptide ligands expressed at the surface of follicular helper T cells. Recently, we have shown that pCons-induced CD8⁺Ti suppress autoimmunity in a murine model of SLE in a manner dependent on *Foxp3* expression [10, 16, 17]. Following pCons administration, CD8⁺ Ti display a unique genetic profile, with upregulated genes including *Foxp3*, *Trp53*, *Bcl2*, *CCR7*, *IFNAR1*, and *IFI202b* and downregulated genes including

regulator of G protein signaling proteins (RGS2, RGS16, and RGS17), glutamic pyruvate transaminase (GPT2), BAX, programmed cell death-1 (PD1), growth arrest and DNA damage inducible 45 beta (GADD45 β), and phosphodiesterase 3b (PDE3b) [47]. CD8⁺Ti in our tolerance model expressed low levels of PD1, CTLA4 and CD122, and a partial characterization of the genetic basis of their suppressive capacity indicates some dependence on the expression of FoxP3, PD1, and IFI202b [10, 16, 17, 19]. However, as yet not all the critical genetic elements required for the full spectrum and function of suppressive activity in this cell population has been elucidated.

3. Cellular, molecular, and functional basis for gene selection in tolerance model

While SLE and related autoimmune diseases are known to be complex and polygenic, not all the susceptibility genes are either sufficient or required for disease progression. Furthermore, some genes regarded as susceptibility genes when expressed in effector T or B cells, e.g., upregulated anti-apoptotic (bcl2) and downregulated apoptotic genes (Bax, GADD45 β), may be advantageous in the activation and suppressive actions of CD8⁺Ti when expressed in these cells. Presumably, certain genes involved in important T cell functions, such as those mediating chemokine/cytokine receptor trafficking or signaling, (e.g., *IFNAR*, *Ifi202b*, *CCR7*) could prove to be crucial for the suppressive effects of CD8⁺Ti. Our recent data highlight multiple genes whose products appear to be advantageous in these cells. We will next discuss further the salient genes we have identified in microarray analyses [47], offering insights into their possible roles in immune tolerance and autoimmunity. Validation of our results by RT-PCR and protein expression studies has substantiated the likelihood that these genes play roles in autoimmunity.

IFI202b

IFI202b is an interferon inducible gene. We have found significant increased expression of ifi202b in tolerized CD8⁺Ti cells [19]. This increased expression lasted at least four weeks after pCons tolerance. Upregulation of the IFN-inducible gene *Ifi202b*, is significant because: **a)** in B cells, *Ifi202* upregulation protects them from apoptosis and predisposes NZB mice to SLE [48], **b)** we and others have demonstrated that the “profile” of peripheral blood cells from SLE patients exhibits multiple upregulated genes under the control of interferons [49, 50], and **c)** recent experiments show that deficiency of IFN γ R2 (surface receptor for type II IFN) in MRL/lpr/lpr mice prevents SLE, whereas knockout of *IFN γ RI* (type I IFN receptor) accelerates the disease [51]. Another gene in the IFI200 cluster, *Ifi202a*, has recently been shown to be dispensable for B cell function [52]. A recent study has found that female and male sex hormones differentially regulate the expression of *Ifi202* within the Nba2 interval of C57BL/6 mice [53]. Female sex hormone 17- β estradiol upregulates, and male sex hormone androgen decreases, *Ifi202* expression. The *Ifi202* gene product has also been reported to bind to p53 and prevent its effects on the expression of pro-apoptosis genes [54]. Thus, the role *IFI202b* of is complex and more studies are needed before its role can be elucidated.

Bcl-2 (B cell lymphoma 2)

Bcl-2 is an important apoptosis regulatory gene. Bcl-2 has been implicated in many cancers [55, 56]. Association between *Bcl2* polymorphism and SLE has been reported [57]. We previously demonstrated that apoptosis was significantly decreased in tolerized CD8⁺Ti cells [10]. We have found increased expression of Bcl-2 in tolerized CD8⁺ Ti cells in BWF1 mice [58]. Similarly, others have found increased expression of Bcl-2 and Bcl-XL in a model of immune tolerance in SLE [59, 60]. Our work and that of others reinforce the concept that Bcl-2 plays an important role in regulating and shaping the T cell repertoire and

immune tolerance by inhibiting programmed cell death in specific T cell subsets including CD8⁺Ti [61]. This probably allows the suppressive cells to survive long enough to produce clinically significant suppression of effector T and B cells.

p53

p53, a tumor suppressor gene, is a DNA-binding transcription factor that acts to regulate the cell cycle and plays an important role in control of cancer. Mutations at the *p53* gene lead to cancer [62]. P53 has been linked to SMAD/TGFβ interactions that promote cell senescence [63], and has multiple effects, both positive and negative, on cell cycle arrest and apoptosis [63, 64]. The p53 protein has recently been shown to play major roles in infectious diseases and immunity [65], and its gene is located in a human gene region linked to SLE [66]. Its levels are increased in lymphocytes from SLE patients compared to controls [67] and in one ethnic group a polymorphism of p53 is associated with SLE [68]. A recent study identifies the major role of p53 in the increased formation of exosomes, a non-classical protein secretion pathway, by upregulated expression of the target gene *TSAP6* [65, 69]. We detected increased expression of p53 in CD8⁺Ti [58]. Conceivably, p53 may play a novel role in support of CD8⁺Ti-mediated tolerance by promoting the exosome-mediated delivery of TGFβ or other key growth factors.

Foxp3

Foxp3 is a master regulator and it plays a significant role in the development and function of Treg. It is a marker for both natural and induced Treg. In humans, mutation in the Foxp3 gene leads to immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) syndrome [70]. In mice, Foxp3 deficiency (The Scurfy mouse) is associated with lymphoproliferation (ref). Whereas **Foxp3** is known to be critical to the function of Treg [71], not all of the important signaling pathways are yet understood [72]. Indeed, Foxp3 either down- (as in most cases) or upregulated [73] by virtue of its high-affinity binding to a specific consensus binding site, ATAAACAA, in its target genes. Upregulation of Foxp3 in rodent CD8⁺CD28⁻ Ti may induce CD4⁺ Treg [74]. TGFβ upregulation of Foxp3 expression [75] identified a new role for this growth factor in immunosuppression. Foxp3 expression CD4⁺ regulatory T cells) was decreased in the absence of CD8⁺ Treg, demonstrating a functional link between the two subsets of Treg in which, CD8⁺CD28⁻ Treg are required for the optimal expansion and function of peptide hCDR1 induced CD4⁺ Treg in murine lupus [45, 76, 77]. We have found increased expression of Foxp3 in CD8⁺ Ti cells, and silencing of Foxp3 with siRNA abrogates the suppression of anti-DNA Ab induced by CD8⁺ Ti cells [10, 17]. These data indicate that Foxp3 plays an important role in the suppression of anti- DNA Ab in murine SLE.

Selected **downregulated** genes in our model of tolerance will be discussed here due to their known roles in autoimmunity [78, 79].

Regulator of G protein signaling (RGS) genes

RGS proteins are potent GTPase-activating proteins (GAP) for heterotrimeric G protein (Gq, Gi, and Go family) alpha subunits, acting as multifunctional inhibitors of signal transduction in many cells [80, 81]. They are also capable of “fine-tuning” GPCR signaling in lymphocytes [82]. In particular, *RGS2*, a growth-inhibitory protein, plays a role in leukemogenesis [83]. Semplicini et al reported that reduction of RGS2 signaling increases Ca²⁺ mobilization and ERK1/2 activation in response to GPCR stimulation [84]. We found that multiple RGS proteins are downregulated in tolerized CD8⁺Ti cells [58].

GPT2

GPT2, is an alanine transaminase, that has a role in gluconeogenesis and amino acid homeostasis, and is an enzyme/biomarker [85] that is upregulated in disease states. GPT2 is implicated in exacerbating autoimmune disease [86], and its levels were shown to be increased in NZB/NZW F1 mice [87]. Increased serum aminotransferases have been reported to be associated with anti-mitochondrial antibodies in SLE patients with autoimmune liver disease [88]. We have found decreased GPT2 mRNA and protein expression in CD8⁺Ti from tolerized BWF1 mice [58].

PDE3b

PDE3b was downregulated in CD8⁺ Ti. Foxp3 binding to its conserved site within the first intron of the PDE3b gene potentially represses expression of this negative signaling regulatory enzyme. *PDE3b* is involved in controlling the abundance of cyclic adenosine monophosphate (cAMP) and plays an important role in the suppression of T cell function [89]. The downregulation of PDE3b has been associated with enhanced insulin secretion, suggesting that secretion of other factors could also be positively modulated. Consistent with the notion that reversal of its cAMP-degrading activity is important for maintenance of CD8⁺Ti, PDE3b is one of the most down-regulated genes in Treg [89].

Bax

The Bcl-2-associated X protein (Bax), is a protein of the Bcl-2 family. It promotes apoptosis by competing with Bcl-2. The expression of *BAX* is upregulated by p53 and Bax has been shown to be involved in p53-mediated apoptosis. The *Bax* gene has also been implicated in lupus nephritis [78]. Decreased expression of Bax has been demonstrated in active SLE patient PBLs compared to inactive or normal controls [90]. However, recent reports showing increased apoptosis and higher expression of Bax and caspase-3 in kidney cells in human lupus nephritis (LN) suggests that apoptosis might be induced through these protein pathways, possibly with resultant tissue damage that plays a role in lupus nephritis progression. [91]. The Bax gene has also been linked to cancer and aging [92, 93]. Altered Bax expression and decreased apoptosis in bone marrow cells of lupus-susceptible NZB/W mice has been reported [94]. We have found decreased expression of the *Bax* gene both at the mRNA and protein level in CD8⁺ Ti [58]. The Bax protein forms heterodimers with bcl-2 protein, which bind to the voltage-dependent anion channels (VDAC) in mitochondria and induce loss of membrane potential and release of cytochrome c to the cytoplasm. Our data showing upregulation of Bcl2 and downregulation of Bax in CD8⁺ Ti may explain the resistance of these induced suppressor cells to apoptosis.

PD1

Programmed cell death 1 (**PD-1**) is an inhibitory receptor known to play an important role in the regulation of autoimmunity and in the maintenance of peripheral tolerance [16, 95, 96]. PD-1 is a member of the CD28/B7 super family of costimulatory molecules that regulates T cell tolerance and is expressed on activated CD4⁺T cells, CD8⁺T cells, and antigen presenting cells (APCs) [95, 97]. PD1 has two ligands, PD ligand 1 (PD-L1) and PD-L2, both of which are type I transmembrane proteins, yet their expression patterns differ [98–100]. PD-L1 is constitutively expressed on murine T cells, B cells, macrophages, dendritic cells (DCs), mesenchymal stem cells, and bone marrow-derived mast cells, and is further upregulated in a number of these cell types upon activation [101]. Expression of PD-L2 is restricted to macrophages, DCs, bone marrow-derived mast cells, and peritoneal B1 cells [95, 97, 101–103].

PD-1-deficient mice develop spontaneous autoimmune diseases including SLE (nephritis and autoantibodies in C57BL/6 mice and cardiomyopathy in Balb/c mice), indicating an essential function of PD-1 in immune tolerance mechanisms [96, 104, 105]. Studies have suggested that PD-1/PD-L1 interaction plays a key role in downregulating the activation of T cells [106]. Blockade of PD-1 has been shown to lead to a worsening of symptoms in murine models of graft-versus-host disease [107] and Experimental Autoimmune Encephomyelitis (EAE) [108]. In contrast, we have shown that blockade of PD-1 protects lupus-prone mice from disease [109]. PD-1 mediated peripheral tolerance involves CD4⁺CD25⁺ T regulatory cells (Treg), which have been shown to highly express both PD-1 and PD-L1 [110]. We have shown that there is reduced expression of PD-1 in inhibitory CD8⁺T cells (CD8⁺Ti) compared to non-inhibitory CD8⁺ T cells following tolerization with the pCons peptide [16]. However, inhibiting expression of PD-1 even more with specific siRNA abrogates the ability of the cells to suppress. Thus, expression of a small quantity of PD-1 is required for the cells to be inhibitory, but expression of high amounts is associated with inability to suppress [16]. We also found that blocking of PD-1 decreased FoxP3 expression in CD8⁺Ti cells from tolerized mice indicating cross regulation [16]. PD-1 is also important in inducing Treg as well as in the mechanisms of action of other suppressive/inhibitory T cell populations [111–113].

4. Conclusions

Peptide tolerance can induce specific CD8⁺ Ti or regulatory cells with a unique gene signature. Silencing of selected genes abrogates the suppression induced by regulatory CD8⁺T cells. Interferon and apoptosis gene signatures are characteristic of a protective phenotype in regulatory CD8⁺ Ti cells. Peptide tolerance induces distinct gene signature including both up and down regulation of selected genes in our tolerance model. Some of the gene signature changes may play a significant role in lupus pathology and could have the potential to aid in the development of future therapeutics.

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Take-home messages

- Regulatory CD8⁺T cells are heterogeneous in mode of induction, phenotype, and function. Their regulation depends on tolerance mechanisms and treatment regimens.
- Peptide tolerance, corticosteroids and various epigenetic agents can alter the gene signature in CD8⁺ T cells.
- Interferon- and apoptosis-related genes can be induced in lupus cells with peptide tolerance and other epigenetic agents such as histones and vitamin A metabolites.
- Both up and down regulated genes are equally important in “resetting” immune responses in SLE.