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T cells, murine chronic graft-versus-host disease and autoimmunity

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Abstract

The chronic graft-versus-host disease (cGVHD) in mice is characterized by the production of autoantibodies and immunopathology characteristic of systemic lupus erythematosus (lupus). The basic pathogenesis involves the cognate recognition of foreign MHC class II of host B cells by alloreactive CD4 T cells from the donor. CD4 T cells of the host are also necessary for the full maturation of host B cells before the transfer of donor T cells. CD8 T cells play critical roles as well. Donor CD8 T cells that are highly cytotoxic can ablate or prevent the lupus syndrome, in part by killing recipient B cells. Host CD8 T cells can reciprocally downregulate donor CD8 T cells, and thus prevent them from suppressing the autoimmune process. Thus, when the donor inoculum contains both CD4 T cells and CD8 T cells, the resultant syndrome depends on the balance of activities of these various cell populations. For example, in one cGVHD model (DBA/2 (C57BL/6xDBA/2)F1, the disease is more severe in females, as it is in several of the spontaneous mouse models of lupus, as well as in human disease. The mechanism of this female skewing of disease appears to depend on the relative inability of CD8 cells of the female host to downregulate the donor CD4 T cells that drive the autoantibody response. In general, then, the abnormal CD4 T cell help and the modulating roles of CD8 T cells seen in cGVHD parallel the participation of T cells in genetic lupus in mice and human lupus, although these spontaneous syndromes are presumably not driven by overt alloreactivity.

Keywords

Chronic GVHD; CD4 T cells; CD8 T cells; Systemic lupus erythematosus

1. Introduction

Systemic lupus erythematosus (SLE) is characterized by a spectrum of autoantibodies that targets multiple normal cellular components, particularly nucleic acids or proteins that are physiologically bound to nucleic acids. Although SLE is highly diverse in its manifestations, a common theme is the loss of B cell tolerance to these cellular autoantigens [1]. More than for any other human condition, several spontaneously arising mouse models for SLE have been described, beginning with the New Zealand strains in 1959 [2,3]. These models are largely genetic [4]. In some cases, an individual gene such as *fas* or *Yaa* plays a major role

in driving the loss of tolerance. However, in general the genetic contribution is complex and involves multiple loci, which are not yet fully defined [4]. Where the issue of environmental influences has been addressed, it has been found that the fundamental disease process is not dependent on exogenous stimuli, but the severity of particular manifestations can be influenced [5]. It has also been striking that multiple targeted genetic manipulations of normal mice, including both traditional transgenes that lead to overexpression and site-directed transgenes that delete an active gene, have been described as models of SLE [6]. In these cases, as well as in the spontaneous models, the specificities of the autoantibodies can vary, as well as the timing of disease onset, the severity of the manifestations, and the degree of clinical involvement, particularly in the kidneys.

Despite extensive investigations, the failures in immunoregulation that underlie these genetic SLE models remain poorly understood [7]. It is not known for sure which B cell tolerance checkpoints are breached in a given model, and why. The autoantibody response to DNA, Sm, and other autoantigens resembles the normal response to exogenous antigens: it involves clonal expansion, somatic mutation, and a pattern of isotype use characteristic of a T-cell dependent immunization [8,9]. Thus the cellular dynamics of the response may be basically normal. Yet the B-cell repertoire is abnormally autoreactive. This may be due to B cell intrinsic defects. In the case of some of the single gene models that target B-cell specific genes, the B cell must be primarily involved. In some of the spontaneous multigenic models, it can be shown that the genetic abnormalities must be present in the B cells for tolerance to be lost [10]. In other cases, however, at least some of the genetic defects lie outside the B cells, *i.e.*, they are B-cell extrinsic [11]. This applies to single gene models that target T cells, antigen presenting cells, or even enzymes or cell surface receptors that would influence the handling of autoantigens [6]. Nevertheless, each of these separate types of genetic defects results in a pattern of autoimmunity that mimics some important aspects of human SLE.

1.1. T cells and experimental SLE

In this review we wish to focus more on the role of the T cell in SLE. As stated above, the loss of B cell tolerance in SLE does appear in general to require the participation of T cells. Multiple T cells abnormalities have been described in human and in murine SLE, although in most cases it is not clear if these are primary or secondary manifestations. Nevertheless, it is striking how difficult it has been to demonstrate definitively the specificity of the T cells that provide help for autoantibody production [12].

As an alternative approach to the study of the numerous genetic murine models for SLE, a small number of experimental protocols have been found to produce a similar spectrum of autoantibodies. These include challenge with certain chemical agents, such as heavy metals or pristane, and the allogeneic interaction of T cells and B cells that are MHC diverse (Table 1). In all these cases, normal mice are made to become autoimmune and their B cells lose tolerance to typical SLE autoantigens, such as DNA and chromatin. We have been particularly interested in two chronic graft-versus-host disease (cGVHD) models over the last several decades (see Table 2). In one, DBA/2 strain spleen cells are injected into (C57BL/6 $\times$ DBA/2)F1 (B6D2F1) recipients (Fig. 1) [13]. In the other, C57BL/6 (B6) spleen cells are injected into bm12 recipients or *vice versa* (Fig. 2) [14]. In both cases, the autoimmunity and immunopathology of SLE appears relatively rapidly over a period of several weeks. In both of these models it is clear that the fundamental abnormality is the allorecognition of host B cells by the donor T cells, even though neither cell lineage is intrinsically 'autoimmune'. This permits these models to be manipulated to elucidate the mechanisms of loss of B cell tolerance, including the kinds of T–B interactions that can contribute to this process.

It should be understood that the cGVHD models in mice are models of human lupus, but not models of human cGVHD. Human cGVHD is a serious problem following allogeneic bone marrow transplantation. The pathology involved, which effects mainly skin, liver and gut, is more similar to acute GVHD in mice [15].

We do not believe that such allorecognition underlies most spontaneous SLE, either human or murine. Some authors have indeed argued that microchimerism (for example, the persistence of fetal cells in a parous female) might lead to a chronic GVHD with autoimmune manifestations, but the significance of this phenomenon remains controversial [16–18]. In addition, we have postulated that an alteration (*e.g.*, somatic mutation) of an MHC class II molecule would mimic the alloreactivity of the cGVHD, but this proposal remains an untested speculation [19]. Nevertheless, the characteristics of the autoantibody response in cGVHD is quite parallel to that seen in spontaneous SLE, in terms of specificities, isotype, clonal expansion, and somatic mutation [20,21]. Therefore, it is highly likely that the mechanisms whereby B cell tolerance is lost in the cGVHD overlap significantly with some of the mechanisms operative in spontaneous SLE, which themselves are likely to be multiple. The T–B collaboration is anomalous because it involves an allorecognition, but the abnormal T cell help that is thereby provided appears to have functional consequences quite reminiscent of what occurs in spontaneous SLE. Thus an understanding of the mechanisms involved in this alloreactivity, and the B cell responses to it, should provide important clues into the fundamental immunopathophysiology of SLE.

2. T cells in the cGVHD

2.1. Donor CD4 T cells

The key cellular mechanism in the cGVHD that results in the loss of B cell tolerance and the production of the autoantibodies typical of SLE is the cognate interaction of CD4 T cells with an MHC class II determinant on the B cell surface. A variety of protocols have achieved this interaction (Table 2). In general, either the donor/recipient strains are paired in such a way that they only differ at the MHC class II loci, or the CD4 cells are isolated free of CD8 cells that would recognize MHC class I [22]. If the allorecognition involves both CD4 T cell interaction with MHC II and CD8 interaction with MHC I, an acute GVHD occurs, which is immunosuppressive, rather than immunostimulatory [23]. The DBA/2 $\Rightarrow$ (C57BL/6 $\times$ DBA/2)F1 (B6D2F1) and the BALB/c $\Rightarrow$ (BALB/c $\times$ A/J)F1 models are exceptions to this rule [24]. The former has been investigated extensively for a deficiency in CD8 cytotoxic lymphocytes, as will be discussed in detail below (Section 2.3).

The MHC class II recognition may be at either the I-A or the I-E locus. However, the autoantibody specificities seen and the degree of immunopathology differ depending on the locus targeted. In one set of experiments, F1 mice were bred between either B6 or co-isogenic bm12 mice and B10.A(2R) or B10.A(4R) MHC recombinant congenics [25]. The MHC class II of B6 is I-A^b, while that of bm12 is I-A^{bm12}. These two alleles differ by only three amino acids, which is sufficient for a full strength MLR (mixed lymphocyte reaction) between the two strains [26,27]. Otherwise B6 and bm12 are identical. B10.A(2R) and B10.A(4R) differ only by the expression of I-E in the former strain, but not in the latter strain. Thus, donor/recipient combinations could be employed that provided for allogeneic differs only at I-A, only at I-E, or at both loci. I-A recognition led to renal disease, while I-E recognition produced higher levels of autoantibodies and anti-Sm autoantibodies in particular. In another set of experiments, DBA/2 spleen cells were transferred into F1 hybrids made by crossing DBA/2 with B10 mice congenic for various MHC haplotypes [28]. In this case, only recognition of the I-A^b haplotype produced renal disease, although all strain combinations produced comparable levels of autoantibodies. These results indicate that the specificity of T–B recognition is important for the nature of the resultant

autoimmune syndrome. However, it was still not clear what precise determinants the alloreactive T cells were recognizing, *i.e.*, what were the peptides in the binding grooves of the MHC molecules that most likely were essential for the formation of the full epitope that bound the T cell receptor.

The MHC class II specific T–B interaction does appear to be cognate, in the sense that the B cells that are driven to lose tolerance must themselves bear the recognized MHC II determinant. Specifically, if (B6 × bm12)F1 mice are lethally irradiated and reconstituted with bone marrows from parental B6 and bm12 strains, so as to produce mixed chimeras, then the transfer of B6 CD4 T cells will cause only the bm12 B cells to produce autoantibodies, while transfer of bm12 CD4 T cells will cause only the B6 B cells to produce autoantibodies [29]. There was no evidence for a bystander effect. Again, the specific recognition of B cell class II appears to be key, but the role of bound peptide remains obscure.

Results from Busser et al. further delineate the requirements for this MHC class II recognition [30]. Utilizing several transgenic mouse strains that express a more or less constricted CD4 autoreactive repertoire, they showed that a diverse repertoire was essential to the production of SLE autoantibodies by MHC II recognition. On the other hand, the non-specific, early polyclonal B cell activation phase of cGVHD occurred even with a limited CD4 repertoire. They speculated that the diverse repertoire requirement could be due to the rarity of the necessary T cell specificity; the requirement for more than one specificity of T cell to interact with low density epitopes on the B cell; a requirement for interaction with several B cells through epitope spreading; or a necessity for functionally diverse T cells. Other laboratories have shown that the persistence of donor CD4 T cells in the recipient is necessary for the continued production of autoantibodies [31].

The antinuclear antibody isotype produced in cGVHD is strongly skewed towards IgG2a (or IgG2c in a *b* allotype mouse) [32]. This parallels what is seen in most spontaneous mouse SLE models, but contrasts clearly with the strong IgG1 isotype predominance found in T-dependent responses to exogenous antigens. This skewing further strengthens the supposition that the cellular interactions that result in loss of B cell tolerance in cGVHD model are similar to those that occur in spontaneous disease.

2.2. Host CD4 T cells

It is possible that the host's CD4 T cells might also play a role in cGVHD, particularly since the recipients are not irradiated or immunosuppressed in any manner before cell transfer. In fact, we found that B6 recipients that were CD4 deficient (CD4 knock outs) were completely resistant to cGVHD [33]. Not only did they not make autoantibodies after the transfer of bm12 CD4 T cells, but their B cells showed no evidence of activation either by phenotypic changes or the production of hypergammaglobulinemia. Surprisingly, this deficient response could not be corrected by the co-transfer of purified B6 CD4 T cells along with the bm12 CD4 T cells. A series of experiments utilizing the autologous reconstitution of B cells after sublethal irradiation (500 r) or the transfer of purified B cells into immunodeficient (*rag1*^{−/−}) recipients, each followed by challenge with bm12 CD4 T cells, indicated that recipient CD4 T cells needed to be present during the ontogeny of host B cells, but that their presence was unnecessary at the time of the initiation of cGVHD [34]. Somehow the host CD4 T cells 'nurtured' the developing B cells such that they became capable of responding to allogeneic help. This nurturing was IL-4 dependent, but it apparently did not require cognate interaction, as a mono-clonal (TCR transgenic) CD4 T cell population was fully capable of this process. Importantly, the requirement for B cell nurturing also extends to their ability to respond to T cell help in response to an exogenous antigen (ovalbumin), although we do not further understand the mechanism (unpublished data).

2.3. CD8 T cells

2.3.1. Donor CD8 T cells: primary donor anti-host CD8 CTL abort lupus

expression—As outlined above, CD4 T cells are necessary and sufficient for inducing the lupus-like features of chronic GVHD, when they are transferred into an MHC II disparate host. If CD4 and CD8 T cells are transferred into an F1 host that is both MHC I + II disparate, the lupus-like chronic GVHD phenotype is altered to an acute GVHD phenotype consisting of lymphopenia, immune deficiency and, in some transfers, early mortality (reviewed in ref. [13]). The B6D2F1 has been an instructive host in this regard, as transfer of whole spleen cells from the B6 parent (B6→BDF1) induces acute GVHD, whereas transfer of CD8 depleted B6 splenocytes converts the phenotype to chronic lupus-like disease, because of the central role of donor CD4 T cells in lupus induction [19]. Surprisingly, transfer of the DBA/2 parental splenocytes into the BDF1 induces chronic GVHD, rather than the expected acute GVHD. This outcome results from defective maturation of DBA/2 CD8 CTL effectors, due at least in part to an intrinsic CD8 T cell defect. In fact, DBA/2 splenocytes have a ~10 fold reduction in the anti-F1 precursor CTL (pCTL) frequency compared to that of B6 mice [24]. BALB/c mice also exhibit a significant reduction in anti-F1 CD8 pCTL frequency compared to B6 mice, and accordingly BALB/c→(BALB/c × B6) F1 (CB6F1) mice exhibit chronic GVHD compared to B6→CB6F1 acute GVHD mice [35]. Thus, chronic GVHD requires donor CD4 T cell activation by allogeneic host MHC II coupled with a relative failure of donor CD8 T cell activation.

The initial two-week kinetics have been characterized for both acute B6→BDF1 and chronic DBA/2→BDF1 GVHD mice and demonstrate differences in CD8 T cell activation within the first few days [36,37]. At days 2–5 after transfer in B6→BDF1 mice, both CD4 and CD8 donor T cells undergo strong proliferation, with >80% of surviving donor cells exhibiting at least one division by day 4. Similar results are seen for donor CD4 T cells in DBA/2→BDF1 mice; however, DBA CD8 T cell proliferation is reduced (<50% of cells with at least one division). Interestingly, this early defective DBA CD8 CTL maturation may reflect an extrinsic defect in DBA CD4 T cell help [36,37]. In B6→BDF1 mice, donor CD8 CTL effector function is first detectable *ex vivo* at day 7 [38] and manifested *in vivo* as a decline in CD4 driven B-cell population expansion that occurs from days 3–7. DBA→F1 mice exhibit a similar proliferation of B cells during this same time, but in the absence of donor CD8 CTL maturation, there is no subsequent decline in host B cells [36]. Serum IFN- γ peaks at day 7 and is largely CD8 T cell derived (both donor and host) [39]. Donor CD8 T cell numbers peak at approximately day 10 and intracellular IFN- γ , TNF α , perforin, along with extracellular FasL, KLRG-1 and CD107a (a marker of CTL degranulation) expression are maximal during the day 7–10 window in both donor and host CD8 T cells [36,37,40,41]. CD80 upregulation on donor CD4 and CD8 T cells peaks at ~ days 10–12 and acts to limit effector numbers [40]. From days 12–14, both expanded donor subsets undergo contraction, mediated in part by upregulated Fas [32], although other molecules (PD-1, etc) also likely contribute.

CD8 α + dendritic cells (DC) have a well-recognized role in promoting CD8 CTL [42]; however, both CD8 α + and CD8 α – DC subsets expand significantly in B6 BDF1 mice, peaking at day 10 [36]. Host DC (both CD8 α positive and negative) and host B cells, T cells and CD11b+ cells all undergo CD4 driven proliferation during days 0–10, but by day 14 their levels that have either returned to control or are significantly reduced vs. control, as a consequence elimination by donor CD8 CTL function.

In summary, donor CD4 T cells activated by host MHC II provide cognate help for host B cells to initiate lupus. If donor CD8 T cells are also transferred, donor CD4 T cells provide for help for CD8 CTL effector maturation, possibly by direct contact but also by activating (licensing) host DC. Donor CD8 CTL specific for host allogeneic MHC class I then mature

and abort donor CD4 T cell driven lupus, primarily by eliminating host B cells, although host T cells and APC are also eliminated. The donor anti-host CTL mediated phase is near complete by two weeks after transfer, and mice exhibit a “cytotoxic phenotype”, characterized by profound elimination of host lymphocytes and engraftment of both donor CD4 and CD8 T cells (reviewed in [43]). In contrast, DBA BDF1 chronic GVHD mice exhibit a two week stimulatory phenotype characterized by significant expansion of host lymphocyte populations, particularly B cells, engraftment of donor CD4 (but not CD8 T cells) and elevated levels of autoantibodies including anti-ssDNA ab (reviewed in ref. [43]). Lupus-specific autoantibodies (anti-dsDNA, anti-PARP) are readily demonstrable beginning at about four weeks [44].

2.3.2. Host CD8 T cells: early downregulation of donor CD8 T cells—A

reciprocal host-vs-graft (HVG) response is also initiated during the first two weeks after transfer and mediated by both host NK and CD8 T cells. The latter exhibit both proliferation and host anti-donor killing that peaks at around day 10 [36,45,46]. Transfer of parental CD8 T cells alone, *i.e.* in the absence of parental CD4 T cells typically does not result in acute GVHD phenotype, since donor cells are efficiently eliminated by the HVG. However, if host NK cells are depleted prior to transfer, donor CD8 T cells engraft and eliminate host B cells by two weeks, albeit incompletely [36]. Presumably such helper-independent CD8 CTL effectors are induced directly by MHC I disparate host DC. Moreover, donor CD8 T cell expansion in the absence of donor CD4 T cell help can be potentiated by directly licensing (*i.e.*, activating) host DC with agonist anti-CD40 mAb [36].

The host CD8-mediated HVG is strongly dependent on the presence of CD8 T cells in the donor inoculum [46], which is consistent with previous work demonstrating that CD8 T cells and perforin contribute to down regulation of an active CD8 T cell response [47,48]. Nevertheless, an attenuated CD8-mediated HVG also occurs following the transfer of donor CD4 T cells only [46]. The specificity of the HVG-mediating host CD8 T cells is incompletely understood but involves host recognition of donor T cell idiotype specific for host MHC I [49].

2.3.3. Donor CD8 T cells: continued suppression of autoimmunity—

Long term, B6→BDF1 acute GVHD mice do not develop lupus. After two weeks, mature donor CD8 effector T cells attack host organs other than the spleen to induce pathology in the liver, lungs, kidney and skin similar to the phenotype seen in human acute GVHD bone marrow transplant recipients [50]. A subpopulation of donor CD8 CTL that are CD103+ and specific for e-cadherin attack renal tissue and perhaps other organs [51]. The extent of mortality seen depends on the number and source of donor T cells transferred. Larger T cell transfers result in a greater severity of acute GVHD, immune suppression and depletion of lymphocyte and hematopoietic elements at about 2–3 weeks. The outcome is altered with the transfer of unfractionated splenocytes, which contain stem cells that are not present in thymocyte or purified T cell transfers [47]. Long term survival in acute GVHD can thus be favored by the transfer of unfractionated donor splenocytes with relatively low numbers ($<10^7$) of CD8 T cells. If recipient mice survive the acute GVHD nadir, they undergo long term donor (and to a lesser extent, host) lymphocyte re-population and reestablishment of immune competence [52]. Host splenic T and B cells are eliminated and reach a nadir at four weeks; they show a modest recovery after that [52]. Despite the long-term low-level persistence of host B cells, however, B6→BDF1 mice do not show evidence of lupus. Therefore, the two-week cytotoxic phenotype for B6 BDF1 mice is predictive of a lupus-free, but somewhat immunodeficient, state long term. On the face of it, this does not appear surprising, since once most host B cells are eliminated by donor CD8 CTL, it would be expected that immune deficiency and lymphopenia would be long lasting, as in human acute GVHD.

It has been shown that after two weeks, splenic donor CD8 CTLs contract to a much greater degree than do donor CD4 T cells [36]. It is possible that following the contraction of the primary donor CD8 CTL population, the persisting donor CD4 T cells could then provide cognate help to residual host B cells, and the mice would revert to a lupus phenotype. Such an outcome was in fact observed following the transfer of perforin defective donor T cells [53]. At two weeks, mice exhibited an intermediate or mild cytotoxic phenotype, consistent with the loss of one of the two major donor CD8 CTL killing pathways (the other being the Fas/FasL pathway) [41]. It might be anticipated that even the loss of one CTL killing pathway would still permit the development of an acute GVHD, although at a slower rate. Instead, donor CD8 T cell depletion occurred prior to complete elimination of host B cells, and long term, the mice exhibited lupus. These results suggest that lupus can occur in the P (parent) F1 model not only with a complete failure of donor CD8 CTL, but also with a partial or sub optimal primary CD8 CTL response.

2.3.4. Donor CD8 T cells: memory CD8 T cells may maintain lupus remission long term—

A second role for CD8 T cells in preventing lupus was observed following CD40 stimulation [36]. DBA→BDF1 mice that also received an agonist anti-CD40 mAb exhibited an accelerated acute GVHD phenotype, such that the kinetics of donor CD8 CTL activity were observed 2–3 days earlier than in B6→BDF1 mice. Accordingly, the expansion of the CD8α+ DC subset occurred at least 5 days earlier than in B6→BDF1 mice, consistent with direct (CD4-independent) licensing of host DC. Furthermore, anti-CD40 treated DBA→BDF1 mice exhibited near complete elimination of host B cells approximately 2–3 days earlier than in B6→BDF1 mice. Nevertheless, despite this enhanced and accelerated acute GVHD seen with anti-CD40 treatment, DBA→BDF1 mice exhibited a rebound *increase* in autoantibodies at 6–8 weeks. While CD4 T cells have a well-recognized role in induction and maintenance of memory CD8 T cells, these results raise the possibility that CD40 stimulation directly licensed host DC and bypassed the requirement for CD4 help for CTL. On the other hand, CD40-mediated acceleration of the primary CTL response may have come at the expense of long-term memory CD8 T cells. Similarly, Tschetter et al. [35] demonstrated that B6–CB6F1 mice exhibit an early cytotoxic/acute GVHD phenotype and evidence of donor anti-host CD8 CTL activity. Long term, however, the mice reverted to a lupus-like disease. The frequency of B6 anti-BALB/c CD8 precursor CTL was comparable to that of B6 anti-DBA; however, the B6 CD4 anti-BALB/c precursor TH frequency was significantly reduced compared to that seen in B6 anti-DBA. Although memory CD8 T cell phenotype was not directly examined in either study, taken together these results raise the possibility that: 1) memory (donor) CD8 T cells may be important in maintaining a CD8 CTL-induced remission and preventing the development of lupus; and 2) donor CD4 T cells have a central role in maintaining CD8 memory T cells in the P→F1 model, a role well described in other model systems [54–56].

2.3.5. CD8 T cells are critical for sex-based differences in lupus severity—

In the DBA→BDF1 model, in contrast to what is seen in the bm12→B6 model, female recipients exhibit more severe long-term renal disease, including nephrotic syndrome, than do male recipients [45,57]. Short term (at two weeks), f→F (female donor and female recipient) mice exhibit nearly 2-fold greater engraftment of donor CD4 T cells vs. m→M (male donor and male recipient) mice. In the P→F1 model, lupus is mediated solely by donor CD4 T cells [37]; however, DBA→BDF1 mice exhibit a lupus phenotype despite the transfer of both CD4 and CD8 T cells, due to a relative failure of DBA CD8 T cells to mature into anti-host CTL effectors. Thus, the data indicated clearly that in P→F1 mice donor CD8 T cells suppress disease lupus expression. It was quite interesting to observe further that depletion of DBA CD8 T cells prior to transfer into BDF1 hosts abolished the sex-based differences in terms of both the two week DBA CD4 engraftment and the long

term renal disease severity. Unexpectedly, however, both sexes of recipients receiving DBA CD8 depleted T cells exhibited the milder, male phenotype. A similar masking of short-term sex differences in donor CD4 T cell engraftment was observed if IFN- γ was blocked *in vivo* [46]. Thus, both long term and short-term sex-based differences are critically dependent on a *disease-augmenting* effect of donor CD8 T cells, and IFN- γ production is contributory. The mechanism was shown to involve an initial weaker donor CD8 CTL GVH and reciprocal HVG response in females, followed by impaired homeostatic contraction of female donor CD4 and CD8 T cells [46]. In contrast, males exhibit a stronger initial donor anti-host CTL and HVG CTL response, which results in rapid and strong homeostatic contraction of donor T cells. In the P→F1 model, upregulation of Fas on donor T cells is strongly IFN- γ dependent [41], and Fas upregulation is a major contributor to donor T cell contraction post activation [37]. Thus, the significantly greater peak IFN-gamma; production by male DBA→BDF1 mice vs. females most likely contributes to greater donor T cell contraction in males. Conversely, female DBA→F1 mice have a reduced IFN- γ levels, reduced donor T-cell contraction and significantly greater residual two-week engraftment of disease-inducing donor CD4 T cells. Importantly, these sex-based differences segregate with the sex of the host and not the donor [58]. Thus, inherent sex-based differences in CD8 CTL generation contribute to lupus severity long term and raise the possibility that the female predominance in human lupus might be related in part to a potentially weaker CD8 CTL response.

2.4. Cytokines

Recently, IFN α and IL-21, have been strongly linked to lupus pathogenesis, although their exact role is not understood. Moreover, both cytokines exhibit pleiotropic effects on both cell mediated and humoral immunity, further complicating our understanding [59,60]. DBA BDF1 mice exhibit markedly elevated (>20-fold over control) splenic IL-21 gene expression for both males and females during the second week of disease. By day 14, however, female levels rise further and are significantly greater than for males [46], and this sex-based difference persists over the long term. By contrast, milder elevations in IFN α related genes are seen, with a peak at around day 7 that is significantly greater for males vs. females. Long term, no significant elevation over control in splenic IFN α related genes was observed. These results provide stronger support for IL-21 than for IFN α in lupus pathogenesis in DBA→BDF1 mice.

2.5. Regulatory T cell (Treg) function

The complex and rapidly advancing field of Tregs has not been well studied in cGVHD models. In DBA→B6D2 F1 mice, pre-treatment of donor CD4⁺, CD25⁺ Tregs prior to transfer with a depleting anti-CD25 mAb converted chronic GVHD phenotype to acute GVHD [61]. These results support the counterintuitive idea that lupus could result from normal Treg suppression of potentially beneficial downregulatory CD8 T cell responses and that blocking Treg function could be beneficial in lupus. Work by Zheng et al. supports the opposite concept, *i.e.* that enhancing Treg function in DBA BDF1 mice is beneficial [62]. In that study, co-transfer of DBA splenocytes plus DBA T cells previously stimulated *in vitro* with allogeneic host (B6) cells plus IL-2 and TGF-beta resulted in suppression of chronic GVHD phenotype. At present, differences in natural or induced Tregs, the presence of absence of Foxp3, or differences CD8 vs. CD4 Tregs have not been directly addressed in cGVHD mice.

2.6. Therapeutic implications of the P→F1 model

The foregoing demonstrates that lupus can result from unchecked CD4 T cell cognate help to a polyclonal population of B cells. CD8 T cells can downregulate this CD4 driven B-cell hyper-activity through CD8 CTL effectors and can maintain remission, possibly through memory CD8 T cells. Whether CD8 CTL actually prevent lupus in normals and fail in lupus

prone individuals is not known; however, data from the P→F1 model suggest that therapeutic induction of CD8 CTL and possibly long term memory cells may be beneficial in preventing or limiting disease expression. The potential major role played by either IFN α and IL-21 in both lupus expression and CD8 CTL function remains to be further defined, but already these cytokines are being targeted in human or murine lupus [63,64].

3. Conclusions

It is not surprising that the T cells have been shown to have diverse roles in the autoimmune cGVHD in mice. Donor CD4 T cells drive the host B cell activation, while host CD4 T cells are required to mature these B cells prior to their encounter with donor T cells. Donor CD4 T cells also help activate donor CD8 T cells, which in turn can downregulate or even ablate the autoimmune response. Donor CD4 T cells license host DC cells, which in turn can interact with donor CD8 T cells. Host CD8 T cells can suppress the activity of donor CD8 T cells, and thereby favor the development of the lupus syndrome. Although the precise mechanisms of T cell participation in spontaneous lupus are still being defined, it seems reasonable to probe these syndromes in humans and in mice for T cell mechanism that have been shown to participate in cGVHD, CD4-B cell interactions almost certainly are central to the pathogenesis of spontaneous lupus, and they have been a target of investigation for several decades. If we understood the peptide specificity of the alloreactive CD4 T cells that drive the formation of the characteristic lupus autoantibodies, we would have a much clearer idea where to look for such epitopes in spontaneous disease. Much less is known about the other T cell activities defined in cGVHD, particularly those that involve CD8 T cells. This area should invite further detailed investigation. For example, the striking role of CD8 T cells in the stronger female disease in the DBA→BDF1 model clearly demands that similar mechanisms be sought for in spontaneous disease.

We are of course very pleased to contribute to this special issue of the *Journal of Autoimmunity* in honor of Pierre Youinou, our colleague, friend, and fellow enthusiast in the quest to understand the mechanisms of autoimmunity.

Abbreviations

cGVHD	chronic graft-versus-host disease
CTL	cytotoxic lymphocytes
DC	dendritic cells
HVG	host-versus-graft

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Fig. 1. Chronic GVHD in bm12→C57BL/6 mice. The MHC of the bm12 donor differs from the MHC of the C57BL/6 recipient just in three amino acids in the I-A class II molecule. Thus donor CD4 T cells recognize MHC II⁺ B cells as foreign. Donor CD8 T cells see only self MHC I. All T cells do not express MHC II. Polyclonal activation and specific lupus autoantibody responses ensue.

Fig. 2. Chronic GVHD in DBA/2 $\rightarrow$ (C57BL/6 $\times$ DBA/2)F1 mice. The MHC of the donor is H-2^d, while the recipient is H-2^{d $\times$ b}. The donor CD8-mediated anti-recipient MHC I is defective, while the donor CD4-mediated anti-recipient MHC II response is normal. Recipient B cells are stimulated and not killed. Polyclonal activation and specific lupus autoantibody responses ensue.

Table 1

Models of experimentally induced SLE in mice.

Model	Protocol	Genetics	Ref
Chronic graft-versus-host disease	Parental CD4 T cells are transferred to unirradiated adult F1 recipients or to MHC II congenic recipients.	Requires donor cells to recognize recipient as MHC II foreign. MHC I recognition must be absent or defective.	[14]
Chronic host-versus-graft disease	F1 spleen cells are transferred to neonatal parental recipients.	Not widely tested. Long term chimerism seen.	[65,66]
Pristane	Hydrocarbon oil is injected i.p. as a single dose.	Generally no genetic restriction, except for certain autoantibody specificities.	[67–69]
Heavy metals (Au, Hg)	Gold thiomalate or mercuric chloride is injected over several months.	Only few MHC loci permit a response, <i>e.g.</i> H-2 ^s .	[70–73]
Certain drugs (<i>e.g.</i> , D-penicillamine or quinidine)	Drug is added to drinking water over several months.	Only few MHC loci permit a response, <i>e.g.</i> H-2 ^s .	[74,75]

Table 2

Protocols for chronic (autoimmune) GVH.

Model	Key Features	Ref
DBA/2 $\Rightarrow$ (C57BL/6 $\times$ DBA/2)F1	Depends on defective CD8 CTL response of donor.	[13]
DBA/2 $\Rightarrow$ (B10 congenics $\times$ DBA/2)F1	Demonstrates role of specificity of MHC II recognition.	[28]
C57BL/6 $\Rightarrow$ (bm12 $\times$ C57BL/6)F1	Autoantibody response skewed to 'lupus' IgG subclasses.	[57]
Bm12 $\Rightarrow$ C57BL/6	Permits parent $\Rightarrow$ parent transfer, and use of multiple transgenics line on the C57BL/6 background.	[57]
C57BL/6 $\Rightarrow$ bm12	Equivalent to reverse transfer (above), but less well studied.	[57]
BALB/c $\Rightarrow$ (BALB/c $\times$ A/J)F1	Depends on defective CD8 CTL response of donor. Less widely studied.	[76]
Host-versus-graft (BALB/c $\times$ A/J)F1 $\Rightarrow$ BALB/c or (BALB/c $\times$ B6)F1 $\Rightarrow$ BALB/c	Requires persistent chimerism. Th2 subclass response (IgG1).	[66]
Transfer between F1's (B6 or bm12 $\times$ B10.A(2R) or B10.A(4R))	Demonstrates role of specificity of MHC II recognition.	[25]
Transfer of purified allogeneic (whole MHC mismatched) T cells	Prevents (CD8-dependent) acute GVHD, and permits chronic GVHD.	
CD4		[37]
Ly1		[14]
CD8 depleted		[19]