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Implications of the parent-into-F1 model for human lupus pathogenesis: roles for cytotoxic T lymphocytes and viral pathogens

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Abstract

Purpose of review—The central role of CD4 T cells in lupus pathogenesis is well recognized; however, the mechanism by which CD4 T cells lose tolerance and promote humoral autoimmunity remains unclear. This review examines mechanisms elucidated in the parent-into-F1 model of lupus and their possible parallels in human lupus pathogenesis.

Recent findings—In the parent-into-F1 model, lupus results from the transfer of normal, foreign reactive CD4 T cells targeted to intrinsically normal F1 B cells. Transfer of normal CD8 T cells prevents lupus, whereas transfer of CD8 T cells with killing defects does not but is correctable with additional in-vivo enhancement of CD8 cytotoxic T lymphocyte (CTL) function. The parent-into-F1 model has two major similarities to Epstein–Barr virus infection: CD4 T-cell-driven polyclonal B-cell hyperactivity and a critical dependence on CD8 CTL for elimination of activated B cells. These similarities are discussed in relation to human lupus pathogenesis.

Summary—Work in the parent-into-F1 model supports the idea that lupus may result from defective CD8 T-cell function and that therapeutic enhancement of CD8 effectors with selective targeting to autoreactive B cells may be beneficial. Despite strong evidence linking Epstein–Barr virus infection with human lupus, the exact nature of this link requires further study.

Keywords

cytotoxic T cells; Epstein–Barr virus; graft-vs.-host disease; lupus

Introduction

Much evidence supports the central role of CD4Tcells in lupus pathogenesis to include the observation that pathogenic IgG auto-antibodies exhibit the hallmarks of a normal antigen-driven response, such as somatic mutation, affinity maturation, and a requirement for T-cell help [1–3]. Moreover, lupus susceptibility genes in humans or mice code for normal alleles rather than for abnormal genes(e.g.oncogenes,mutations),indicating that lupus can result from a normal T-cell-driven humoral immune response that is abnormally targeted to self-antigen [4]. A major unresolved question is the mechanism(s) by which T-cell tolerance is

lost and nuclear autoantigens are targeted. The following review integrates findings from the parent-into-F1 (p→F1) model that sheds light on this question.

Current concepts in human lupus pathogenesis

In human lupus, disease progresses through four theoretical stages (reviewed in [4]): genetic predisposition; induction phase, that is loss of tolerance, characterized by activation of T helper cells; expansion phase, characterized by recruitment and clonal expansion of autoreactive T and B cells; and tissue injury (clinical disease). The events involved in the transition from genetic predisposition to induction phase are poorly understood, but it is generally agreed that nongenetic factors, that is environmental triggers, are required for disease expression as the concordance rate for monozygotic twins is usually reported at less than 50% [5]. The list of environmental triggers associated with human lupus is extensive and includes microbial pathogens and toxins [6]; however, no agent has been definitively identified as causative in human lupus [6].

Progression from induction phase to clinical disease

Regardless of the nature of the inductive event, patients initially exhibit low titer, nonpathogenic T-cell-dependent IgG auto-antibodies [7]. Continued activation of autoreactive T and B cells results in clonal diversification, epitope spreading (expansion phase), and pathogenic auto-antibodies that mediate disease [7–11]. Because the asymptomatic expansion phase can precede clinical disease by years [8], mechanistic studies of these early stages in humans are problematic if not impossible.

Activated autoreactive B cells amplify autoimmunity

B cells contribute to lupus pathogenesis not only by producing auto-antibodies but also by perpetuating and shaping the immune response through reciprocal activation of T cells. As noted by Shlomchik *et al.* [12], activated B cells are potent APC and take up autoantigens through their B-cell receptor (BCR) as a macromolecular complex allowing presentation of any antigenic peptides within that complex. This in turn results in recruitment and activation of a more clonally diverse range of T helper (Th) cells than those responsible for initiating B cell activation. This expanded pool of Th cells then provides help to more clonally diverse B cells, thereby beginning a new cycle of B-cell antigen uptake with further expansion of T-cell and B-cell specificities. This positive feedback cycle provides a mechanistic explanation for clonal expansion and epitope spreading in lupus patients. Importantly, as these authors note, the T cells that initiate B-cell activation need not be self-reactive and after a few turns of the cycle, the presence of the exogenous initiating antigen may no longer be required [12].

Downregulation in lupus

Given the potent amplification mechanism outlined above, breaks in tolerance should invariably lead to autoimmunity; however, experimental tolerance breaks in normal mice result in transient and self-limited autoantibody production without lupus [13–16]. It has been suggested that lupus may be a failure of downregulatory mechanisms that, following exposure to a lupus trigger, normally inhibit progression from induction phase to expansion phase [4].

Summary

The mechanism(s) by which normally quiescent autoreactive T cells escape tolerance and provide help to autoreactive B cells is unknown. Further, it is not clear whether lupus is initiated by activation of foreign-reactive or self-reactive CD4 Th cells, possibly through molecular mimicry. As postulated by Shlomchik *et al.* [12], activation of foreign-reactive

CD4T cells could lead to a break in tolerance if unchecked polyclonal B-cell expansion results. The autoreactive portion of these activated B cells can then present endogenous self-proteins to previously quiescent autoreactive T cells resulting in their activation. Endogenous downregulatory mechanisms may prevent disease amplification in normals and, importantly, they may fail in lupus-prone individuals, permitting pathologic amplification, autoantibody production, and progression to clinical disease.

Essentials of the p→F1 model

The transfer of homozygous parental strain T cells into normal semi-allogeneic F1 hosts (p→F1) results in a graft-vs.-host disease (GVHD) that takes one of two phenotypes. A lupus-like lymphoproliferative phenotype (chronic GVHD) occurs following the transfer of donor CD4 T cells into an MHC II disparate F1 host. The similarity to human lupus in various strain combinations has been well documented (reviewed in [17,18]) and disease results from donor CD4 cognate help to F1 B cells leading to polyclonal B cell activation and lupus-specific auto-antibody production. By contrast, a suppressive/cytotoxic phenotype (acute GVHD) occurs following the transfer of both donor CD4 and CD8 T cells subsets into an MHC I + II disparate F1 host. Disease begins initially as chronic GVHD, that is donor CD4-driven polyclonal host B-cell expansion; however, activation of donor CD8 T cells and their subsequent maturation into effector cytotoxic T cells (CTLs) specific for host MHC I results in elimination of donor CD4 T-cell-expanded host lymphocytes. Donor CD8 CTL also attack host organs in a manner similar to that seen in human acute GVHD following bone marrow transplantation [19]. Thus, donor CD8 CTLs play a critical role in preventing the lupus phenotype. Two exceptions to this general paradigm underscore the role of donor CD8 T cells: DBA/2→(C57Bl/6 × DBA/2)F1 mice and BALB/c→(BALB/c × C57Bl/6)F1 mice [18,20]. In both transfers, mice develop a lupus-like phenotype despite the transfer of both donor CD4 and CD8T cells into an MHC I + II disparate F1. The mechanism in both examples involves defective CD8 CTL maturation [20–22] underscoring the critical role of donor CD8 CTL in the prevention of lupus in this model.

Implications of the p→F1 model in lupus initiation: role of CD4 T cells and B cells

Unlike spontaneous models of murine lupus, in the p→F1 model the exact time of disease onset, the initiating antigen and the mechanism by which tolerance is lost are all known. Clearly, tolerance loss following the transfer of allo-reactive T cells seen in p→F1 mice is artificial and unlikely to represent the mechanism by which tolerance is lost in human lupus, the linkage of maternal-fetal microchimerism with autoimmunity notwithstanding [23]. Once tolerance is artificially broken, however, chronic GVHD mice exhibit a disease that strongly resembles human lupus, particularly that subset of human lupus patients characterized by serum anti-dsDNA ab and renal disease [24•]. Thus, chronic GVHD mice likely illustrate common mechanisms operative in some human lupus patients, particularly in the induction and expansion phases of human lupus. Theoretical extrapolations from the p→F1 model to human lupus are listed below and discussed.

The CD4 T helper cells initiating lupus do not need to be autoreactive

As shown by the p→F1 model, lupus like disease in chronic GVHD mice results from the transfer of alloreactive CD4 T cells. Transferred homozygous parental strain CD4 T cells are intrinsically normal and are seen as ‘self’ by the recipient F1. Because the recipient F1 expresses MHC alloantigens of the opposite parent, donor CD4 T cells recognize all MHC II expressing F1 cells as foreign resulting in cognate help and polyclonal activation of host B cells. Lupus is initiated then not by activation of autoreactive or by intrinsically abnormal

CD4 cells but rather by activation of normal, foreign-antigen-specific T cells aberrantly targeted to all F1 B cells. Alloreactive CD4 Th cells are necessary and sufficient for lupus induction in chronic GVHD mice [18]. It is unclear whether autoreactive CD4 Th cells become subsequently involved following several cycles of alloreactive donor CD4 T cell driven epitope spreading and clonal expansion as proposed by Shlomchik *et al.* [12]. Thus, although autoreactive T cells can induce lupus following adoptive transfer [25], they are not absolutely required for disease initiation.

Lupus can result when all B cells are potential recipients of sustained CD4+ T-cell help

In the chronic GVHD paradigm, all B cells regardless of their antigen specificities are potential recipients of cognate, allo-specific donor CD4 Th cell help. Selective targeting of T cell help to just the autoreactive B cell population is not absolutely required because without exogenous foreign antigen, only self-reactive B cells will encounter their natural BCR ligand (i.e. endogenous self-antigen) and become mature auto-antibody secreting B cells.

A normal B cell repertoire can produce lupus-specific auto-antibodies

Auto-antibodies and lupus-like disease develop in normal, non lupus-prone F1 mice following donor CD4 T cell transfer; however pathogenic auto-antibodies are absent if the B cell repertoire does not develop normally [26]. Although genetic B cell defects can result in pathogenic auto-antibodies [27], the development of lupus in chronic GVHD mice demonstrates that such defects are not absolutely required.

Lupus results primarily from a loss of T cell rather than B cell tolerance

In the p→F1 model, lupus results from an experimentally induced loss of peripheral T cell tolerance. Once T cell tolerance is breached, the presence of normally occurring autoreactive B cells and their ability to produce pathogenic auto-antibodies is unmasked. These results are consistent with the idea that tolerance for lupus autoantigens resides primarily at the T cell level and that normally occurring autoreactive B cells are kept in check by a lack of T cell help due to central and/or peripheral mechanisms.

Implications of the p→F1 model in lupus downregulation: role of CD8 cytotoxic T-lymphocyte

Co-injection of parental CD8 T cells aborts the lupus response early (~2 weeks) before lupus-specific auto-antibodies arise. Thus, CD8 CTL prevents progression to lupus in p→F1 mice by eliminating activated autoreactive B cells. CD8 CTL are first responders in the prevention of lupus and, like the initiating CD4 T cells, need not be autoreactive but instead need only be targeted to the population of activated B cells and include those with autoreactive specificities. In GVHD mice, CD8 CTL are intrinsically normal and are specific for foreign antigen, that is allogeneic MHC I. Donor CD8 CTL arise at the initiation of disease and tolerance loss as opposed to the CD8 Ti described by Singh *et al.* [14] that arise at approximately 1 month after a tolerance break. By targeting allogeneic MHC I, all B cells (autoreactive and foreign-reactive) are eliminated, thereby removing the potential for lupus development but unfortunately at the cost of inducing immunodeficiency.

Failure of CD8 cytotoxic T-lymphocyte to control and/or eliminate B cell activation allows progression to lupus long term

CD8 CTL failure can occur either early (e.g. DBA→BDF1 mice) or weeks to months after an initially acute GVHD phenotype (e.g. B6 perforin knock out→BDF1 mice) [20,28]. Impaired CTL killing allows survival of host B cells, both self-antigen and foreign-antigen

reactive, and following homeostatic downregulation of donor CD8 T cells, surviving host B cells can reexpand upon exposure to donor CD4 T cell help and secrete auto-antibodies.

Remaining questions: how could foreign-reactive CD4 T cells break tolerance and provide cognate help to autoreactive B cells in humans?

For a chronic GVHD-like reaction to occur in humans, it is necessary for autoreactive B cells to be seen as foreign by a clonal population of CD4 T cells. In the p→F1 model, all host B cells are deemed foreign by transferred donor CD4 T cells and are potential candidates for cognate CD4 T cell help. However, only those B cells that also bind their cognate ligand (e.g. autoantigen) will become mature class-switched auto-antibody producing B cells. Thus, it is not necessary to postulate that only autoreactive B cells be candidates for T cell help. Using this analogy, a lupus inducing antigen would need to be capable of entering all B cells in a clonally independent fashion that is regardless of BCR specificity. A putative lupus antigen would then be presented in the context of self MHC II on potentially all B cells thereby creating a disconnect between the BCR specificity and the antigenic peptides recognized by the CD4 Th cells. Cognate help from antigen-specific CD4 T cells would then result in polyclonal B cell activation and auto-antibody production as in the chronic GVHD model.

Similarities between the p→F1 model and human Epstein–Barr Virus infection

The similarities between Epstein–Barr virus (EBV) infection and the p→F1 model are discussed below; however, it should be noted that other agents likely exist that share similarities with the p→F1 model to include endogenous murine viruses and are beyond the scope of this review. For simplicity, we have used EBV as an example of a possible lupus-inducing agent. Importantly, we are not claiming that EBV is in fact a lupus-inducing agent or is the sole agent that could act in this manner but rather that it exemplifies properties similar to the p→F1 model that could result in lupus.

B cell tropism in Epstein–Barr Virus and CD4 T cell help

The EBV receptor CD21 (CR2) is expressed on all B cells and follicular dendritic cells [29]. All B cells are potential targets for EBV internalization, presentation of EBV peptides, and recognition by EBV-specific T cells. As in the p→F1 model, all B cells are therefore potential recipients of cognate help from an oligoclonal population of EBV-specific CD4 T cells and the autoreactive B cell portion could become auto-antibody-secreting cells following encounter with self-antigen recognized by their BCR.

Recovery from Epstein–Barr Virus is strongly dependent on CD8 T cells

The central role of CD8 CTL in the control of EBV is well known (reviewed in [30] and transfer of EBV-specific CD8 CTL has been used therapeutically for control of EBV associated lymphoproliferative conditions [31]. Such transfers are protective for both: 1) EBV associated post transplant lymphoproliferative disease in immunodeficient patients [32]; and 2) EBV positive Hodgkin's disease in normals [33]. By extending the p→F1 analogy, it is possible that incomplete CD8 CTL elimination of EBV-mediated polyclonally activated B cells at the time of CD8 CTL homeostatic contraction could result in persistence of EBV-infected B cells, continued EBV-specific CD4 help for residual B cells and auto-antibody production as outlined for chronic GVHD mice depending on the degree to which autoreactive B cells are infected. Thus, EBV infection exhibits the two major features of the p→F1 model: 1) its ability to render all B cells 'foreign' regardless of their antigenic BCR specificity thereby rendering them susceptible to normal CD4 T cell help and subsequent

polyclonal B cell activation; and 2) the critical role played by CD8 CTL in terminating B cell activation.

Human Epstein–Barr virus infection, lupus and cytotoxic T-lymphocyte

EBV infection has long been linked to human lupus [34] and similarities between human EBV infection and the p→F1 model were noted in 1988 [35]. In the interim, increasing evidence supports the idea that EBV may be a lupus inducing pathogen (reviewed in [36,37,38•]), although this remains controversial. For example, lupus patients exhibit a higher prevalence of EBV infection compared with age matched controls [39]. Moreover, reports of molecular mimicry between the targets of the EBV ab response and targets of the lupus ab response (e.g. Sm, Ro) support the idea that prolonged uncontrolled EBV infection could permit epitope spreading resulting in lupus specific ab production [36,40•]. Indirectly linking EBV infection to lupus is the observation that both entities exhibit polyclonally expanded B cells that could potentially drive further T cell expansion, epitope spreading, and lupus like disease [12].

Of note, lupus patients exhibit evidence of impaired EBV control in the form of higher viral loads and reduced CD8 CTL responses to EBV [41,42]. Although CD8 T cells in normals and lupus patients with EBV infections are similar in phenotype, their frequency tends to be increased and their function decreased in lupus patients [43]. Taken together, these studies support the idea that lupus patients have defective CD8 CTL control of EBV infection. It is not clear however whether defective CD8 CTL function is a primary or secondary event in EBV infected lupus patients. Based on the results discussed above, a prediction from the p→F1 model is the possibility that a characteristic of some lupus-prone individuals is a primary preexisting and predisposing defect(s) in CD8 CTL effector function. Upon exposure to EBV (or an EBV-like agent), such individuals would be unable to completely eliminate EBV infected B cells leading to humoral autoimmunity. The existence of a preexisting primary CTL defect is supported by work by Stohl [44] in which lymphocytes from identical twins discordant for lupus were tested *in vitro* and defects were observed from both the affected and unaffected twin. However, it is well documented that both human and murine lupus are characterized by a disease-associated (secondary) defect in CD8 CTL [42] and in interleukin-2 (IL-2) production (reviewed in [45•]) thereby complicating our understanding of the role of CTL defects in lupus. Thus, it is not possible at present to resolve the conundrum of whether defective CD8 CTL control of EBV infection is secondary to a lupus-associated CTL defect and/or is a further manifestation of a preexisting (and predisposing) primary CTL defect. The observation that lupus patients exhibit defective CD8 CTL responses to both EBV and CMV [41] indicates a global rather than antigen-specific defect in CTL function but does not distinguish whether such a defect is primary or secondary. This question will be difficult to address in human studies. Nevertheless, regardless of the exact nature of the CTL defect, the foregoing studies suggest that therapeutic enhancement of CTL in lupus patients might improve not only EBV clearance but also lupus symptomatology. In support of this idea, recent work in the p→F1 model demonstrates that in-vivo CTL enhancement is not only feasible but also beneficial (reviewed in [46•]).

Conclusion

Lupus can be initiated in mice by normal, foreign reactive CD4 Th cells abnormally targeted to all B cells. If unchecked, sustained CD4 T cell-driven polyclonal B cell activation can result in lupus. CD8 T cells, in addition to their well recognized roles in allograft rejection, tumor immunity, and intracellular virus infection, may also have a novel role in controlling expansion of B cells and preventing autoimmunity through both perforin and Fas/FasL

pathways as demonstrated in chronic GVHD mice [47]. These results raise the possibility that CD8 CTL may act in humans as an early mechanism capable of limiting breaks in tolerance (possibly induced by EBV or an EBV-like agent) and preventing evolution to lupus. Failure of such a CD8 CTL protective mechanism may characterize a subpopulation of lupus-prone individuals. Regardless of whether CD8 CTL impairment plays a primary role in addition to a secondary role in lupus pathogenesis, it is possible that promotion of CD8 CTL specific for the lupus-inducing antigen might be therapeutically beneficial.

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References and recommended reading

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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