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CTLA4Ig Alters the Course of Autoimmune Disease Development in Lyn−/− Mice

Sarah A. Oracki,* Evelyn Tsantikos,† Cathy Quilici,‡ Amanda Light,* Thomas Schmidt,* Andrew M. Lew,* Joanne E. Martin,‡ Ken G. Smith,§ Margaret L. Hibbs,‡ and David M. Tarlinton*

Lyn-deficient (Lyn−/−) mice develop an age-dependent autoimmune disease similar to systemic lupus erythematosus, characterized by the production of IgG anti-nuclear Ab. To determine the extent to which this autoimmune phenotype is driven by T cell costimulation, we generated Lyn−/− mice expressing a soluble form of the T cell inhibitory molecule, CTLA4Ig (CTLA4Ig). Surprisingly, although CTLA4Ig prevented myeloid hyperplasia, splenomegaly and IgG anti-nuclear Ab production in Lyn−/− mice, it did not inhibit immune complex deposition and tissue destruction in the kidney. In fact, regardless of CTLA4Ig expression, Lyn−/− serum contained elevated titers of IgA anti-nuclear Ab, although generally IgA deposition in the kidney was only revealed in the absence of self-reactive IgG. This demonstrated that activation of autoreactive B cell clones in Lyn−/− mice can still occur despite impaired costimulation. Indeed, CTLA4Ig did not alter perturbed Lyn−/− B cell development and behavior, and plasma cell frequencies were predominantly unaffected. These results suggest that when self-reactive B cell clones are unimpeded in acquiring T cell help, they secrete pathogenic IgG autoantibodies that trigger the fulminant autoimmunity normally observed in Lyn−/− mice. The absence of these IgG immune complexes reveals an IgA-mediated axis of autoimmunity that is not sufficient to cause splenomegaly or extramedullary myelopoesis, but which mediates destructive glomerulonephritis. These findings have implications for the understanding of the basis of Ab-mediated autoimmune diseases and for their treatment with CTLA4Ig. The Journal of Immunology, 2010, 184: 757–763.

Lyn tyrosine kinase is a critical proximal initiator of BCR signaling and has the nonredundant function of engaging inhibitory mechanisms to downmodulate this signaling (1). Lyn is therefore a significant regulator of BCR signaling thresholds and has a decisive role in determining the outcomes of B cell development.

Lyn is the predominant Src-family kinase expressed in B cells and myeloid cells, where it is involved in signaling downstream of integrins, cytokine receptors, FcRs, and receptor tyrosine kinases (1–3). Importantly, Lyn is not expressed in T cells (2). In its absence, B cells are hyperresponsive to BCR stimulation, with elevated intracellular calcium mobilization and hyperphosphorylation of Akt and MAPK pathway members (1). B cell tolerance fails in Lyn−/− mice triggering a severe autoimmune disease analogous to systemic lupus erythematosus (SLE) in humans (4), and indeed, B cells from the majority of SLE patients are reported to have insufficient Lyn activity (5, 6). We and others have characterized the prominent aspects of the Lyn−/− phenotype including splenomegaly, an expansion of the myeloid compartment, renal tissue damage, elevated serum Ig levels including IgG anti-nuclear Abs (ANAs), and plasmacytosis (4, 7, 8).

Several mechanisms may contribute to the development of the Lyn−/− phenotype. Self-reactive B cells are usually anergized or deleted during development (9), and Ab reactive to self-Ags does not normally appear in significant amounts (10). A failure of B cell tolerance in Lyn-deficient mice may trigger autoimmunity that is then compounded by T cell involvement and inflammatory processes. In a cyclic manner (11), inflammation caused by autoantibodies exacerbates tissue damage and causes further release of self-Ags, activating autoreactive B cells to secrete Ab and present Ag to T cells. Autoantibodies are deposited in immune complexes on the surface of macrophages and dendritic cells through complement- and FcRs (12, 13). In this way, DNA and other self-Ags can be brought into contact with dendritic cell TLRs, activating them and allowing priming of specific T cells (14). Indeed, Lyn-deficient mice that are unable to signal in response to DNA ligation of TLR9 have a greatly diminished autoimmune phenotype (15). We hypothesized that T cells, activated by presentation of self-Ag, amplify and mature autoantibody production and drive inflammatory processes that compound the autoimmune phenotype of Lyn−/− mice. To determine whether impeding the connection between T cells and autoimmune B cells would interfere with the disease process, we crossed Lyn−/− mice with mice that transgenically express a soluble form of CTLA4 (termed CTLA4Ig/Lyn−/−). This CTLA4Ig is a fusion between the extracellular domain of CTLA4 with the Fc portion of the mouse IgG2c to aid solubility and is secreted from pancreatic islets under the rat insulin promoter. Circulating CTLA4Ig (~100 µg/ml) outcompetes CD28 binding to CD80/CD86, obstructing T

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Abbreviations used in this paper: ANA, anti-nuclear Ab; IgAN, IgA nephropathy; SLE, systemic lupus erythematosus.
cell costimulation and therefore impairing T cell-dependent B cell activation in transgenic mice (16). In keeping with this, transgene-derived CTLA4Ig has been reported to ablate B cell responses following immunization with a T cell-dependent Ag and to prevent humoral responses to allogeneic islet grafts (17, 18). In addition, CTLA4Ig is under trial for use as a therapeutic in human SLE patients (19). Constitutive exposure to CTLA4Ig, although not mimicking a short-term, therapeutic regimen, provides a means for determining its potential to ameliorate chronic immunological abnormalities, such as those that develop in Lyn−/− mice. Many abnormalities that occur in Lyn−/− mice were obviated by CTLA4Ig expression, although surprisingly, kidney pathology was not ameliorated. CTLA4Ig did not alter intrinsic Lyn−/− B cell and plasma cell defects, but revealed their capacity to generate IgA-mediated autoimmunity in the absence of IgG immune complexes.

Materials and Methods

Mice

Transgenic mice expressing CTLA4Ig under the control of rat insulin promoter were generated on the B6.C-H-2bm1 (C57BL/6 with the bml mutation of H-2Kb) background and subsequently backcrossed to C57BL/6 (16), Lyn-deficient C57BL/6 mice (4) were bred with CTLA4Ig-expressing mice to generate Lyn-deficient offspring that carry one allele of CTLA4Ig. Lyn−/− mice that express soluble CTLA4Ig (16) (termed CTLA4Ig/Lyn−/−). This inhibitory molecule impairs T cell priming (Supplemental Fig. 1), enabling the resolution of cell-intrinsic aspects of the Lyn−/− phenotype from those that are exacerbated by T cell involvement. It should be noted that T cell activation still occurs in the presence of CTLA4Ig, distinguishing this from models involving T cell deficiency.

Splenomegaly develops early in Lyn−/− mice (7); however, when these mice express CTLA4Ig, splenomegaly is inhibited over their lifespan (Fig. 1A). In Lyn−/− mice, splenomegaly is thought to be due to the increased and abnormal presence of myeloid cells and their precursors in the spleen (8, 22). To determine whether the expansion in myeloid precursors present in Lyn−/− mice persists when CTLA4Ig is expressed, we measured colonies of myeloid cells that formed after culture of bone marrow and spleen cell suspensions with a range of CSFs. Colony-forming cells in the bone marrow are increased in Lyn−/− mice compared with Lyn-sufficient controls and are not significantly reduced by CTLA4Ig (Fig. 1B). In the spleen and blood (data not shown), wild-type animals contained no myeloid progenitor cells, but Lyn deficiency resulted in mobilization of precursor cells to these peripheral compartments. Demonstrating that T cell-mediated processes are a major contributor to the dysregulated myelopoiesis in Lyn−/− mice, CTLA4Ig resolves this, although the modest increase in myeloid progenitor cells in CTLA4Ig/Lyn−/− mice relative to wild-type was

![FIGURE 1. Splenomegaly and extramedullary myelopoiesis in Lyn−/− mice](http://www.jimmunol.org/)

### Results

CTLA4Ig prevents splenomegaly and myeloid hyperplasia in Lyn−/− mice

To determine the contribution of CD28 T cell costimulation to the development of autoimmunity in mice lacking Lyn, we generated Lyn−/− mice that express soluble CTLA4Ig (16) (termed CTLA4Ig/Lyn−/−). This inhibitory molecule impairs T cell priming (Supplemental Fig. 1), enabling the resolution of cell-intrinsic aspects of the Lyn−/− phenotype from those that are exacerbated by T cell involvement. It should be noted that T cell activation still occurs in the presence of CTLA4Ig, distinguishing this from models involving T cell deficiency.

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presumably due to the absence of Lyn in these cells or their precursors rather than the result of T cell activity in Lyn−/− mice. These data imply that the perturbed myelopoiesis in the Lyn−/− spleen is predominantly a result of T cell-driven inflammatory processes, whereas in the bone marrow, the increase in myeloid progenitors is probably caused by defects intrinsic to the Lyn-deficient cells.

Lyn−/− kidney pathology is not inhibited by CTLA4Ig

Mice lacking Lyn develop severe autoimmune glomerular pathology (4, 7). To determine the extent to which the nephropathy observed in Lyn−/− mice requires costimulation, we examined kidney sections for pathology and complement deposition. Immunofluorescence staining showed that CTLA4Ig diminished the deposition of IgG and C3 in Lyn−/− glomeruli. Despite this, CTLA4Ig expression did not improve glomerulonephritis in Lyn−/− kidneys (Fig. 2A), as lobularity, crescent formation, and hypercellularity (as indicated by overlapping mesangial cell nuclei; Fig. 2B) were equally evident within CTLA4Ig/Lyn−/− glomeruli. Because autoreactive IgA is also able to form immune complexes and induce nephropathy, we measured IgA deposition in kidney tissue sections and found that CTLA4Ig/Lyn−/− glomeruli were positive for IgA (Fig. 2A). Serum titers of ANA showed a similar pattern of isotype preference (Fig. 2C). In contrast, sera from both Lyn−/− and CTLA4Ig/Lyn−/− mice contained very high titers of IgA ANA from an early age (Fig. 2D). These findings demonstrate that despite its ability to ameliorate splenomegaly and myeloid hyperplasia, CTLA4Ig does not prevent renal pathology and unmasks a costimulation-independent IgA-mediated arm of humoral autoimmunity in Lyn−/− mice that is otherwise outcompeted by IgG.

Perturbed Lyn−/− B cell development and behavior are independent of costimulation

B cell selection and maturation are influenced by local lymphoid microenvironments that are in turn influenced by autoimmune inflammatory processes. The persistence of ANA in CTLA4Ig/Lyn−/− mice reveals a failure to delete or anergize autoreactive B cell clones and suggests that Lyn−/− B cell differentiation is intrinsically defective regardless of the environment in which the cells develop. To evaluate whether impairing T cell costimulation alters Lyn−/− B cell development, we used flow cytometry to delineate B cell populations in lymphoid tissues of the mice. The proportions of pre−/pro-B, immature and transitional B cells in the bone marrow of both Lyn−/− and CTLA4Ig/Lyn−/− mice did not differ substantially from wild-type controls (Fig. 3A). However, mature recirculating B cells were severely diminished in Lyn−/− bone marrow regardless of CTLA4Ig expression. The elevated proportion of plasma cells, as revealed by Syndecan-1 expression and measured by flow cytometry, in Lyn−/− bone marrow and spleen was also independent of T cell costimulation as it occurred identically in Lyn−/− and CTLA4Ig/Lyn−/− mice (Fig. 3C, 3D).

Despite being enlarged, spleens of Lyn-deficient mice contain a diminished proportion of T2, marginal zone, and follicular B cells and an increase in plasma cell frequency relative to C57BL/6 controls. These changes also occur in the spleens of Lyn−/− mice that express CTLA4Ig (Fig. 3B, 3D), which are normal in size, demonstrating that the changes in B cell populations are intrinsic defects in cell survival or differentiation in the absence of Lyn. Among Lyn−/− splenic B cells, however, is a population expressing low amounts of CD21 but high for surface IgM (Fig. 3B). This population does not appear in spleens of either C57BL/6 or CTLA4Ig/Lyn−/− mice, suggesting its appearance may depend on disease status in what is currently an unknown way.

Lower BCR surface expression is assumed to be a general feature of B cells that lack negative regulators of BCR signaling and consequently downregulate surface Ig to compensate for elevated signaling (23). Indeed, Lyn−/− B cells have lower levels of BCR surface expression than C57BL/6 B cells (23). To estimate the activation status of Lyn−/− B cells in the presence of CTLA4Ig, we used flow cytometry to measure surface IgM levels and intracellular calcium flux in response to BCR ligation (Fig. 4). IgM surface expression is equally reduced on Lyn−/− and CTLA4Ig/Lyn−/− follicular B cells relative to Lyn-sufficient cells, indicating that B cells lacking Lyn experience elevated BCR signaling.

**FIGURE 2.** CTLA4Ig attenuates IgG autoantibody production in Lyn−/− mice but not glomerular pathology or IgA autoantibodies. A, Formalin-fixed kidney sections from 5-mo-old mice were stained with H&E to examine histopathology (magnification ×200). Tissue sections are representative of at least eight mice of each genotype. Deposition of complement, IgG, and IgA in glomeruli of mice of the indicated genotypes was detected by staining frozen kidney sections from 5-mo-old mice with fluoresceinated Ab or biotinylated Ab, followed by avidin-FITC, and observed on a Zeiss Axioplan 2 microscope (magnification ×200). B, Overlapping mesangial cell nuclei were counted in the lobules of a minimum of seven glomeruli from at least four 5-mo-old mice per genotype. C, IgG ANAs were measured by ELISA and detected using a combination of secondary Abs recognizing IgG1, IgG2b, IgG2c, and IgG3 isotypes. The OD is shown in arbitrary units. D, IgA ANAs were detected as above using biotinylated anti-IgA Abs.
regardless of CTLA4Ig expression (Fig. 4A). In support of this, we found that ligation of the BCR induced delayed but elevated calcium flux in CTLA4Ig/Lyn\(^{-/-}\) follicular B cells relative to C57BL/6 B cells, identical to that typical for Lyn\(^{-/-}\) B cells (Fig. 4B). The defects in BCR signaling and the changes in B cell populations in Lyn\(^{-/-}\) mice are therefore due to the absence of Lyn in those cells and are not affected by an altered immunological environment.

**Isotype switching of Lyn\(^{-/-}\) B cells is largely unaffected by CTLA4Ig**

An additional defining feature of the Lyn\(^{-/-}\) phenotype is the accumulation of plasma cells in the bone marrow and spleen, with Lyn-deficient mice having up to 10-fold more plasma cells than C57BL/6 mice (4). Flow cytometry revealed the proportion of Lyn\(^{-/-}\) plasma cells to be significantly elevated regardless of CTLA4Ig expression (Fig. 3). To determine whether the Ab class restriction of plasma cells was also unaffected in the transgenic animals, plasma cell isotypes were examined by ELISPOT assay (Fig. 5). IgM-secreting plasma cell frequencies were not reduced in CTLA4Ig/Lyn\(^{-/-}\) bone marrow, suggesting that the formation of these cells is independent of processes requiring costimulation and that their persistence does not require inflammation-induced survival niches (Fig. 5A). Although the Lyn\(^{-/-}\) spleen contained a significantly lower proportion of IgM-secreting plasma cells when CTLA4Ig was expressed (Fig. 5B), it remained substantially elevated compared with C57BL/6. Hyperresponsiveness of autoreactive IgM-expressing B cells does not intrinsically result in switching to pathogenic IgG isotypes (24, 25). Indeed, the proportions of Lyn\(^{-/-}\) plasma cells secreting IgG of various subtypes did not generally differ from C57BL/6 and nor were they remarkably altered by CTLA4Ig expression (Fig. 5). Changes in the concentrations of IgG subtypes in the serum were also minor (Fig. 6). A generalized but modest CTLA4Ig-induced reduction in plasma cell frequency was observed for IgG2c, IgG2b, and IgG3 isotypes, indicating either a direct or indirect requirement for CD28 T cell costimulation for their production (Figs. 5, 6). Consistent with a previous report on serum titers (7), IgA-secreting plasma cell frequencies in the spleen of Lyn\(^{-/-}\) mice were elevated irrespective of the costimulation blockade (Fig. 5B), and serum titers of IgA were even higher in CTLA4Ig/Lyn\(^{-/-}\) mice than in their nontransgenic Lyn\(^{-/-}\) littermates (Fig. 6). Thus, plasmacytosis in Lyn\(^{-/-}\) mice appears to be because of a cell-intrinsic capacity to accumulate and persist in the absence of Lyn. This particularly applies to plasma cells of autoreactive specificities that secrete IgA autoantibodies irrespective of the availability of T cell help.

**Discussion**

The study of Lyn’s role within specific cell types is complicated by the development of Ab-mediated autoimmunity in mice lacking this negative regulator of signaling. Lyn-deficient mice develop splenomegaly and myeloexpansion, high-serum IgG ANA titers,
we generated Lyn through their interaction with self-reactive B cells (26, 27), may be particularly important in compounding the autoimmunity other cell types into the process of disease development. As T cells which are due to cell-extrinsic factors, including the recruitment of occur as a direct result of the loss of Lyn in particular cells and previously been unclear which aspects of the Lyn mediated axis of disease in the Lyn indicated.

**FIGURE 4.** B cell hyperresponsiveness is intrinsic to the loss of Lyn. A. Lyn−/− follicular B cells express lower levels of IgM on their surface relative to wild-type B cells, regardless of T cell activity. Bars represent mean fluorescence index (MFI) ± SE of at least three mice, and significant differences are shown relative to C57BL/6 mice unless otherwise indicated. B. Calcium flux was measured in follicular B cells (CD19+/CD23+ CD21+IgM+) for 5 min in response to stimulation with 25 μg/ml anti-IgM F(ab′)2 fragment. Results are representative of three experiments.

and renal pathology with glomerular deposition of IgG immune complexes and complement (4, 7, 8). This disease phenotype is probably triggered by a combination of defects in myeloid cells and a failure to select against self-reactive B cells. However, it has previously been unclear which aspects of the Lyn−/− phenotype occur as a direct result of the loss of Lyn in particular cells and which are due to cell-extrinsic factors, including the recruitment of other cell types into the process of disease development. As T cells may be particularly important in compounding the autoimmunity through their interaction with self-reactive B cells (26, 27), we generated Lyn−/− mice that express CTLA4Ig to provide an in vivo mechanism of inhibiting T cell priming in this model. We reasoned that CTLA4Ig would reduce the contribution of costimulation-dependent processes to disease development and delineate Lyn-related defects from those that are compounded by T cell involvement. CTLA4Ig does not block absolutely T cell activation but rather moderates the degree or extent to which this occurs. This clearly distinguishes this model from those lacking T cells completely.

CTLA4Ig is of interest as a therapy for lupus nephritis (19), and contrary to our expectations, lifelong exposure to CTLA4Ig did not prevent glomerular tissue destruction in Lyn−/− mice. This renal pathology may result from defects in glomerular endothelial cells, which normally express Lyn (33). In addition, the persistence of autoreactive Lyn−/− B cell clones is not affected by CTLA4Ig and in the relative absence of pathogenic IgG, IgA autoantibodies seem to predominate as the major isotype-precipitating humoral autoimmunity. This indicates an intrinsic failure to negatively select or anergize autoreactive B cells (9, 34), although this aspect of the Lyn−/− phenotype is evidently compounded and matured by T cell involvement.

CTLA4Ig expression did not rescue defects in Lyn−/− B cell development and behavior, as Lyn−/− mice and their transgenic CTLA4Ig/Lyn−/− littermates both had a deficiency of T2, marginal zone, and follicular B cells in the spleen and an excess of IgM-secreting plasma cells in the spleen and bone marrow (1, 4). Polyclonal B cell hyperactivation is a hallmark of lupus (35), and

**FIGURE 5.** Effect of costimulation in determining Ab-secreting cell frequencies in Lyn-deficient mice. The frequency of splenocytes secreting Abs was measured by ELISPOT assay using isotype-specific capture and detection Abs. Graphs show the mean values ± SE of at least three mice of each genotype. Significant differences are shown relative to C57BL/6 mice unless otherwise indicated.
expression of CTLA4Ig. Although interestingly, Lyn


less of the immune environment. Despite IgM plasma cells being present at the same frequency in bone marrow and spleen, CTLA4Ig reduced Lyn


CTLA4Ig to impede IL-6–driven IgA production in CTLA4Ig/


IgM serum levels presumably by preventing splenomegaly. No significant differences were detected in the frequencies of plasma cells secreting IgG isotypes, although interestingly, Lyn


The CTLA4Ig/Lyn


TNF family, in which IgA but not IgG autoantibody production is T cell dependent (42). This finding highlights the variability in mechanisms that may underlie disease development in otherwise superficially similar models. CTLA4Ig has been shown to not prevent IgA switching in certain immune responses (43), whereas the requirement for T cells in IgA switching may be overridden by B cell production of IL-6 (44). Levels of IL-6 are strongly correlated with IgAN disease severity (45, 46) and we have found that deletion of IL-6 in Lyn


IgA nephropathy (IgAN), the most common primary glomerulonephritis leading to end-stage renal failure in humans, and the related condition Henoch-Schonlein purpura (39). IgAN is characterized by glomerular hypercellularity and inflammation associated with the glomerular deposition of IgA1 and, less prominently and consistently, IgG, IgM, C3, and C4. There is evidence for T cell involvement and active IgAN is associated with high titres of serum IgA (40, 41). It is intriguing that the CTLA4Ig transgene converts a lupus-like IgG-dominated renal disease to one closely resembling IgAN. It could be that such modulation of the T cell response biases in favor of IgA deposition, or that reduced IgG production biases the Ab response in favor of IgA (perhaps by increasing the number of extramucosal plasma cell niches available for IgA production). Another model of autoimmune disease mediated by IgG and IgA autoantibodies is mice transgenic for the B cell activating factor belonging to the


FIGURE 6. Serum Ig titers in autoimmune and CTLA4Ig-transgenic Lyn


Our results show that mutations in B cells that trigger autoimmunity, such as Lyn deficiency, are not adequate to drive fulminating autoimmunity in these models. Instead, chronic stimulation of autoreactive lymphocyte specificities in a situation where tolerance has been breached, coupled to an inability to resolve inflammation, potentially lead to the cyclical exacerbation and compounding of the phenotype into an advanced state of autoimmunity (11). Following from this, previous studies have assumed that the cycle of Ab-mediated autoimmunity may be interrupted by selectively ablating individual pathways involved. For example, disease development has been intercepted at the level of B cell activation, B cell maturation, cytokine signaling, and T cell activation. Despite the disparate nature of these facets of disease development, disruption of a single one superficially appears to attenuate disease (47–54). Additional mutations in Lyn


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REFERENCES


