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Defective Autoimmune Regulator-Dependent Central Tolerance to Myelin Protein Zero Is Linked to Autoimmune Peripheral Neuropathy

Maureen A. Su,‡ Dan Davini,† Philip Cheng,*, Karen Giang,‡ Una Fan,‡ Jason J. DeVoss,‡,§ Kelsey P. A. Johannes,† Lorelei Taylor,‡ Anthony K. Shum,‡ Mariella Valenzise,‖ Antonella Meloni,‖ Helene Bour-Jordan,† and Mark S. Anderson†

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common acquired chronic autoimmune disease characterized by peripheral nerve demyelination and dysfunction. How the autoimmune response is initiated, identity of provoking Ags, and pathogenic effector mechanisms are not well defined. The autoimmune regulator (Aire) plays a critical role in central tolerance by promoting thymic expression of self-Ags and deletion of self-reactive T cells. In this study, we used mice with hypomorphic Aire function and two patients with Aire mutations to define how Aire deficiency results in spontaneous autoimmune peripheral neuropathy. Autoimmunity against peripheral nerves in both mice and humans targets myelin protein zero, an Ag for which expression is Aire-regulated in the thymus. Consistent with a defect in thymic tolerance, CD4+ T cells are sufficient to transfer disease in mice and produce IFN-γ in infiltrated peripheral nerves. Our findings suggest that defective Aire-mediated central tolerance to myelin protein zero initiates an autoimmune Th1 effector response toward peripheral nerves.

The online version of this article contains supplemental material.

Materials and Methods

Mice

NOD.AireGW/+ mice were generated as previously described (2). NOD.scid mice were purchased from The Jackson Laboratory. Mice were housed in a pathogen-free barrier facility at University of California, San Francisco and at the University of North Carolina, Chapel Hill. Clinical neuropathy and diabetes were assessed as described previously (6). For the group of mice used in neuropathy incidence studies, mice that developed diabetes were maintained on insulin (i.p. injection daily) until 22 wk of age. NOD.AireGW/+ mice with clinical neuropathy were used as serum and splenocyte donors. Experiments complied with the Animal Welfare Act and the National Institutes of Health guidelines for the ethical care and use of animals in biomedical research.

Histology/electron microscopy

H&E staining was performed as described in (2). Immune infiltration was scored in a blinded fashion with 0, 1, 2, 3, and 4 scores indicating no, <25, 25–50, 50–75, and >75% infiltration, respectively. Luxol fast blue staining was performed as described previously (7). Toluidine blue staining and transmission electron microscopy was performed on sciatic nerve sections from mice perfused with 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M cacodylate buffer. Toluidine blue staining was performed on semithin sections of epoxy-embedded sciatic nerves. Transmission electron microscopy was performed as described (in Ref. 8).

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Indirect immunofluorescence

Immunofluorescence staining was performed using diluted (1:600) mouse and human sera on OCT-embedded NOD.scid sciatric nerve sections as described previously (9).

Immunohistochemistry

Stains for immune cells in OCT-embedded sciatric nerves were performed with anti-CD4 (GL1.5; BioXCell), anti-CD8 (YTS169; BioXCell), and anti-F4/80 (BM8; eBioscience) Abs as described (in Ref. 9).

Adoptive transfer

Adoptive transfer of whole spleen and lymph node cells from neuropathic NOD.AireGW/+ mice was performed as described previously (6). Diabetic NOD.AireGW/+ mice were excluded as donors. For each NOD.scid recipient mouse, 10 × 10⁶ whole spleen and lymph node cells were transferred. CD4+ and CD8+ T cells were isolated by staining with CD4-FITC (Southern Biotechnology Associates) and CD8a-APC-Cy7 (BD Biosciences). Populations were purified using a MoFlo (DakoCytomation) cell sorter and plated in the presence of anti-CD3 and anti-CD28 (1 μg/ml in PBS) for 96 h. For some experiments, anti-CD4 and anti-CD8 microbeads (Miltenyi Biotec) were used for positive selection on an MS or LS column. A total of 7 × 10⁶ CD4, 7 × 10⁶ CD8, or 3 × 10⁶ CD8 T cells was transferred. Cotransfers of 7 × 10⁶ CD4 and 7 × 10⁶ CD8 T cells were also performed.

Intracellular cytokine staining

Infiltrating immune cells were isolated from sciatric nerves by mincing and digestion in 2 mg/ml collagenase. Cells were stimulated with PMA/ionomycin and stained as described (in Ref. 9).

Immunoblot/immunoaffinity purification

Sciatic nerve extracts were prepared in CHAPS buffer. Immunoblots and immunoaffinity purification were performed as described (in Ref. 10).

Mass spectrometry

For the last 24 h, 1 g/ml IL-2 (20 U/ml) was added to culture. A total of 7 × 10⁶ CD4, 7 × 10⁶ CD8, or 3 × 10⁶ CD8 T cells was transferred. Cotransfers of 7 × 10⁶ CD4 and 7 × 10⁶ CD8 T cells were also performed.

FIGURE 1. Hypomorphic Aire mice spontaneously develop autoimmune peripheral neuropathy. (A) Neuropathy curve of female NOD.AireGW/+ (AireGW/+) mice and female NOD.WT (WT) littermates. (B) Clasping of hind limbs in neuropathic NOD.AireGW/+ mouse indicating bilateral weakness that is not seen in NOD.WT mice. (C) Representative H&E-stained, formalin-fixed, longitudinal sections of sciatric nerves from an NOD.WT and NOD.AireGW/+ mouse at 22 wk of age (original magnification ×20). (D) Cumulative infiltration scores of sciatric nerves from NOD.WT and NOD.AireGW/+ mice. Each symbol represents an individual mouse. *Significant difference between the two groups. (E) Luxol fast blue-stained longitudinal sections of sciatric nerves from NOD.WT and NOD.AireGW/+ mice for the presence of myelin. Arrows point to areas of demyelination (original magnification ×20). Images are representative of four independent experiments. (F) Toluidine blue-stained cross sections of NOD.WT and NOD.AireGW/+ sciatic nerves (original magnification ×40) for the presence of myelin. Images are representative of at least three independent experiments. (G) Electron micrograph of sciatric nerves shown in (F). Arrows point to myelinated axon in NOD.WT, and demyelinated axon in NOD.AireGW/+ nerve (original magnification ×1100). Images are representative of at least three independent experiments.
Radioligand binding assay

Human P0 cDNA clone (IMAGE) was in vitro transcribed and translated with \(^{35}\text{S}\) labeling and assays performed as described (9). Autoantibody index was calculated as \([\text{cpm sample} - \text{cpm negative control}] / \text{cpm positive standard} \times 100\). Samples were positive if \(>3\) SD above mean for healthy control group.

Human subjects

Patients and controls were included in the study after written informed consent was obtained. Study protocol was approved by the institutional review board at University of California, San Francisco.

Statistics

Data was analyzed with Prism software (GraphPad) using unpaired \(t\) tests. Log rank tests were used for comparison of survival curves. A \(p\) value \#0.05 was considered significant.

Results

Hypomorphic Aire mice spontaneously develop autoimmune peripheral neuropathy

By 22 wk of age, \(\sim 80\%\) of female NOD.Aire\(^{GW/+}\) mice develop spontaneous neuropathy (Fig. 1A) (2) that is not seen in wild-type (NOD.WT) littermates. Affected mice display bilateral weakness of the hind limbs that progresses to severe paralysis affecting all limbs (Fig. 1B, Supplemental Video 1). This neuropathy is associated with immune cell infiltration in NOD.Aire\(^{GW/+}\) sciatic nerves (Fig. 1C, 1D), but not in brain or spinal cord (Supplemental Fig. 1A).

Progression of neuropathy is associated with upregulation in sciatic nerves of CXCL10 (IP-10), CCL2 (MCP-1), and CCL5 (RANTES) (Supplemental Fig. 1B), three chemokines that have been linked with inflammatory neuropathies (11, 12). Multifocal areas of demyelination are seen on Luxol fast blue-stained sections of NOD.Aire\(^{GW/+}\) sciatic nerve (Fig. 1E). Additionally, decreased density of myelinated axons is seen on toluidine blue-stained cross sections of sciatic nerve in neuropathic NOD.Aire\(^{GW/+}\) mice (Fig. 1F). Electron microscopy of these same sciatic nerves demonstrates demyelination of individual axons in NOD.Aire\(^{GW/+}\) mice (Fig. 1G). The symmetric nerve dysfunction, mononuclear cells infiltrating peripheral nerves, and multifocal demyelination recapitulate many of the features of CIDP.

In addition to developing autoimmune peripheral neuropathy, NOD.Aire\(^{GW/+}\) mice also develop spontaneous autoimmune diabetes. The incidence of diabetes in NOD.Aire\(^{GW/+}\) mice is the same as in NOD.WT mice (Supplemental Fig. 2A) (2). Histology of sciatic nerves from five diabetic (nonneuropathic) NOD.Aire\(^{GW/+}\) mice did not demonstrate signs of immune infiltration in the sciatic nerve (Supplemental Fig. 2B, 2C). Sera from two diabetic NOD.Aire\(^{GW/+}\) mice were negative for P0 autoantibodies by ELISA (data not shown). Rarely, diabetic NOD.Aire\(^{GW/+}\) mice maintained on insulin also develop neuropathy. Histology of sciatic nerves from two mice with both diabetes and neuropathy demonstrated moderate immune infiltration (Supplemental Fig. 2C).

FIGURE 2. CD4\(^{+}\) T cells are sufficient to transfer autoimmune peripheral neuropathy. (A) Immunohistochemical stains of sciatic nerve from either neuropathic NOD.Aire\(^{GW/+}\) (Aire\(^{GW/+}\)) mouse or NOD.WT (WT) littermate with Abs against CD4, CD8, and F4/80. Images shown are representative of two separate experiments (original magnification \(\times 10\)). (B) Representative H&E-stained, formalin-fixed, longitudinal sections of sciatic nerve from neuropathic mouse (T936) used as donor in adoptive transfer experiments (original magnification \(\times 20\)). Arrow points to areas of dense immune cell infiltration. (C) Donor NOD.Aire\(^{GW/+}\) mice used in adoptive transfer experiments, sex, age, clinical finding, and histological score of sciatic nerves at time of spleen and lymph node harvest. (D) Neuropathy curve of NOD.scid mice receiving activated whole spleen and lymph node cells (10 \(\times\) 10\(^{6}\) cells/recipient; \(n = 8\)), sorted CD4\(^{+}\) T cells (7 \(\times\) 10\(^{6}\) cells/recipient; \(n = 12\)), sorted CD8\(^{+}\) T cells (3 \(\times\) 10\(^{6}\); \(n = 4\) or 7 \(\times\) 10\(^{6}\); \(n = 7\)), or combined CD4\(^{+}\) and CD8\(^{+}\) T cells (7 \(\times\) 10\(^{6}\) of each, \(n = 8\)) from neuropathic NOD.Aire\(^{GW/+}\) donor mice. Cumulative data from four independent experiments are shown. (E) Histological scores of sciatic nerves from recipient mice at the time of sacrifice. Each shape represents an individual mouse. Cumulative data from four independent experiments are shown. Line represents average score. *Significant difference from whole spleen and lymph node transfer (\(p \leq 0.05\)).
CD4+ T cells transfer autoimmune peripheral neuropathy and produce IFN-γ in peripheral nerves

To determine the cellular composition of immune cells infiltrating the PNS of NOD.AireGW/+ mice, we stained sciatic nerves from NOD.WT and NOD.AireGW/+ mice with Abs against CD4, CD8, F4/80, B220, and CD11c cell-surface markers. Within NOD.AireGW/+ nerve infiltrates, CD4+ Th cells and F4/80+ macrophages were more frequent than CD8+ cytotoxic T cells, B220+ B cells, or CD11c+ dendritic cells (Fig. 2A and data not shown). Few cells expressing these markers were seen in NOD.WT nerves.

To demonstrate a cellular basis for the pathogenesis of autoimmune peripheral neuropathy, we transferred spleen and lymph node cells from neuropathic NOD.AireGW/+ mice (between 19 and 34 wk of age) into immunodeficient Prkdcscid/scid NOD mice (NOD.scid mice). Histology of donor sciatic nerves demonstrated immune infiltration in all nerves tested (Fig. 2B, 2C). Eight out of eight recipients of whole spleen and lymph node cells (10 × 10^6 cells per recipient) from neuropathic NOD.AireGW/+ mice developed neuropathy by 10 wk posttransfer (Fig. 2D), suggesting that immune cells are a pathogenic entity.

To determine the relative importance of CD4+ helper and CD8+ cytotoxic T cell subsets, we transferred purified CD4+ and CD8+ populations into NOD.scid recipients. Similar to recipients of whole spleen and lymph node cells (10 × 10^6 cells per recipient) from neuropathic NOD.AireGW/+ mice developed neuropathy by 10 wk posttransfer (Fig. 2D), this finding suggests that CD8+ cells can also transfer neuropathy, but less effectively than CD4+ cells. Finally, eight out of eight recipients of both 7 × 10^6 CD4+ and 7 × 10^6 CD8+ cells combined developed neuropathy by 10 wk posttransfer. The incidence of neuropathy in recipients of both CD4+ and CD8+ cells was not significantly different from either recipients of 10 × 10^6 whole spleen and lymph node cells or from recipients of 7 × 10^6 CD4+ cells (Fig. 2D). Histological examination of sciatic nerves from recipients demonstrated immune infiltration within sciatic nerves in all mice with clinical neuropathy at the time of sacrifice (Fig. 2E).

We stained CD4+ T cells infiltrating NOD.AireGW/+ sciatic nerves for intracellular IFN-γ, IL-4, and IL-17 cytokines to determine the frequency of subsets producing these cytokines. IFN-γ production was seen in ~40% of CD4+ T cells (Fig. 3A, 3B), and IL-4 and IL-17 production was rarely seen (Fig. 3B). No infiltrating CD4+ T cells were detected in NOD.WT sciatic nerves. A comparable percentage of CD4+ T cell subsets were seen in the spleen of NOD.AireGW/+ and NOD.WT mice (Fig. 3C).

Within the sciatic nerves, an average of 1700 IFN-γ–producing CD4+ T cells were isolated from each neuropathic NOD.AireGW/+ mouse (Fig. 3D). In contrast, <100 IL-4– and IL-17–producing CD4+ T cells were present on average in the sciatic nerves. Within the spleen, an average of 5.9 × 10^6 IFN-γ–producing CD4+ T cells was seen in NOD.AireGW/+ mice compared with 2 × 10^6 IFN-γ–producing CD4+ T cells in NOD.WT mice (Fig. 2G).

Fewer than 1 × 10^6 IL-4– and IL-17–producing CD4+ T cells were seen in NOD.AireGW/+ and NOD.WT spleens. Taken together, these data are consistent with a strong Th1 effector response in the sciatic nerves in the model.

P0 is a major Aire-regulated PNS autoantigen

Serum autoantibodies from Aire-deficient mice have been successfully used to identify tissue-specific self-Ags that are targets of autoimmunity (9, 10). On indirect immunofluorescence, serum autoantibodies in neuropathic NOD.AireGW/+ mice react against sciatic nerves in a streaklike pattern (Fig. 4A). Immunoblot with

![FIGURE 3.](http://www.jimmunol.org/)

A. Representative flow cytometry plot of CD4+ T cells infiltrating the sciatic nerves of 18-wk-old neuropathic NOD.AireGW/+ mouse stained for intracellular IFN-γ after activation with PMA/ionomycin. Negative control is CD4+ T cells from same sciatic nerve preparation that have not been activated. Plot is representative of four mice from three independent experiments. (B) Average percent of CD4+ T cells producing IFN-γ, IL-4, or IL-17A in sciatic nerves of NOD.WT or neuropathic NOD.AireGW/+ mice (n = 4 for each group). Each organ was processed separately (not pooled). Data are included from three independent experiments. (C) Average percent of CD4+ T cells producing IFN-γ, IL-4, or IL-17A in spleen of NOD.WT or neuropathic NOD.AireGW/+ mice (n = 4 for each group). Each organ was processed separately (not pooled). Data are average of three independent experiments. (D) Absolute numbers of CD4+ T cells producing IFN-γ, IL-4, or IL-17A in sciatic nerves of NOD.WT or neuropathic NOD.AireGW/+ mice. (E) Absolute numbers of CD4+ T cells producing IFN-γ, IL-4, or IL-17A in spleens of NOD.WT or neuropathic NOD.AireGW/+ mice.
sera from neuropathic NOD.AireGW/+ mice against whole sciatic nerve extract demonstrated an oligoclonal pattern of reactivity in NOD.AireGW/+ sera, which was predominantly against a 25–30-kDa Ag (Fig. 4B). This 25–30-kDa Ag was immunopurified using autoantibodies from sera of NOD.AireGW/+ mice to bind Ags from whole sciatic nerve extract and subjected to peptide mass fingerprinting. Microsequenced peptides derived from the 28-kDa PNS-specific protein P0 with a confidence score approaching 100% (Fig. 4C).

To confirm the specificity of autoantibodies in NOD.AireGW/+ sera for P0, we performed a competition assay in which recombinant P0-MBP tag fusion protein was incubated with serum samples prior to immunoblotting. Titration of increasing concentrations of recombinant P0-MBP fusion protein into serum samples resulted in decreasing intensity of the 25–30-kDa band on immunoblot, whereas the equivalent concentrations of negative control protein (MBP tag alone) did not (Fig. 4D). Furthermore, autoantibodies in sera from NOD.AireGW/+ mice had significantly increased reactivity to P0-MBP fusion protein by ELISA than autoantibodies in sera from NOD.WT littermates (Fig. 4E).

NOD.AireGW/+ mice have a quantitative decrease in the expression of Aire-regulated tissue-specific self-Ags in mTECs (2). Because P0 is a major PNS autoantigen in NOD.AireGW/+ mice, we sought to determine whether P0 is quantitatively decreased in NOD.AireGW/+ mTECs. cDNA generated from sorted mTECs was used to interrogate the relative expression levels of tissue-specific self-Ags in NOD.AireGW/+ compared with NOD.WT mTECs. To validate our cDNA samples, we demonstrated that insulin 2 (Ins2), glutamic acid decarboxylase 67, and P0 in sorted mTECs from NOD.WT and NOD.AireGW/+ mice. Data are normalized to cyclophilin A and relative to NOD.WT. Representative data from at least two independent experiments are shown. Within each experiment, three replicates for each genotype and peptide concentration were performed. Splenocytes from individual mice (not pooled) were used in each experiment. *Significant difference between the two groups.
but not glutamic acid decarboxylase 67, is quantitatively decreased in NOD.AireGW/+ mTECs compared with NOD.WT (Fig. 4F), as has previously been reported (4). Similar to Ins2, P0 expression in NOD.AireGW/+mTECs was ~10% of NOD.WT expression (Fig. 4F).

The decreased expression of P0 in NOD.AireGW/+mTECs led us to hypothesize that autoimmune peripheral neuropathy results from defective negative selection of P0-specific T cells in the thymus. To test this hypothesis, splenocytes from neuropathic NOD.AireGW/+ mice (between 20 and 22 wk of age) were incubated with irrelevant HEL peptide or P0 peptide 180–199. Splenocytes from NOD.AireGW/+ and WT mice proliferated to the same extent in response to HEL peptide (Fig. 4G, left panel). At all three concentrations of P0 180–199, in contrast, NOD.AireGW/+ immune cells proliferated to a significantly greater degree than WT immune cells (Fig. 4G, right panel).

Autoantibody to P0 in APS1 patients

CIDP was recently reported in two unrelated APS1 patients with confirmed mutations in Aire (5). One patient harbored compound heterozygous Aire mutations (R257X/R203X), and the other patient was homozygous for an Aire R139X mutation. The diagnosis of CIDP was based on: 1) weakness, sensory loss, and absent reflexes; 2) evidence of demyelination; and 3) the presence of infiltrating CD4+ T cells and macrophages on nerve biopsy. Surprisingly, autoantibodies against a number of neuropathy-associated Ags were negative (5). Autoantibodies against P0, however, were not previously tested in these patients.

Indirect immunofluorescence using sera from these two patients demonstrated autoantibodies that bound sciatic nerve in a streaklike pattern (Fig. 5A) reminiscent of that seen in NOD.AireGW/+ mice. We then employed a radioligand binding assay to test for P0-specific autoantibodies in the sera from these two patients. Although none of the sera from the healthy controls reacted against P0, sera from the two APS1 patients with CIDP were positive for autoantibodies against P0 (Fig. 5B). Additionally, 2 out of 12 patients with APS1 but without a clinical history of neuropathy also demonstrated serum reactivity to P0, raising the possibility that these patients may be at risk for developing CIDP.

Discussion

In this study, we show that mice and humans with defective Aire function share loss of tolerance to P0, which correlates with the development of spontaneous autoimmune peripheral neuropathy. We show for the first time, to our knowledge, that CD4+ T cells and F4/80-expressing macrophages are also prevalent in the sciatic nerve infiltrates of neuropathic NOD.AireGW/+ mice (Fig. 5E–G). Thus, autoimmune peripheral neuropathy in NOD.AireGW/+ mice resembles human CIDP in immune response and pathological changes in affected nerves.

The identification of P0 as a peripheral nerve autoantigen in Aire deficiency is significant because dominant protein Ag(s) in human autoimmune peripheral neuropathy are not well defined. α and β tubulin, P0, P2, PMP22, and connexin 32 have all been reported to be candidate Ags targeted by the autoimmune response in CIDP (reviewed in Ref. 16). P0 is a peripheral nerve-specific protein that makes up the majority of myelin in the PNS (17). Loss of P0 due to genetic mutations (rather than autoimmune destruction) can result in Charcot Marie Tooth type IB, a heritable demyelinating peripheral neuropathy (Online Mendelian Inheritance in Man 118200). In addition, P0 can induce experimental autoimmune neuritis upon immunization with adjuvant in mice (18) and is an autoantigen in other models of autoimmune peripheral neuropathy (11, 19).

We demonstrate in this study that P0 is an Aire-regulated tissue-specific self-Ag in the thymus and that immune cells in the spleen of Aire-deficient mice have increased reactivity toward P0. These data delineate a model a model in which tolerance toward peripheral nerves is maintained by Aire-mediated upregulation of P0 Ag in the thymus. Negative selection of P0-specific T cells in the thymus prevents escape of P0-reactive T cells into the periphery, which can cause autoimmune peripheral neuropathy. In this study, we did not test whether T cells infiltrating the sciatic nerves of NOD.AireGW/+ mice are also reactive to P0 because of the low number of immune cells that we are able to isolate from sciatic nerves. Further study, including the generation of Ag-specific
clones from infiltrating T cells, will be needed to define the myelin-specific T cell response in the model.

We found that CD4+ T cells were sufficient to transfer neuropathy to immunodeficient mice in a 6–10-wk time frame. Previously, P0-specific T cell lines have been shown to transfer neuropathy into Lewis rats by 6 d (20). The slower kinetics of neuropathy development in our study can potentially be due to multiple factors, including the polyclonal repertoire of the T cells, species-specific differences between mice and rats, and lack of B cells in NOD.scid recipients.

A caveat of this study is the small number of patients with APS1 and CIDP. APS1 is a rare condition with a frequency of much <1 in 100,000 in the North American population. In addition, it appears that CIDP is an infrequent manifestation within APS1 subjects. We have attempted to identify additional subjects with APS1 and biopsy-proven CIDP within larger patient collections available in Scandinavia, but were unable to identify additional patients. Importantly, however, the two patients in this study are unrelated and have different Aire mutations, which strengthens the possibility that our findings are associated with Aire.

Finally, findings in this study may inform the development of more specific and effective immune therapies for autoimmune peripheral neuropathy. Current treatments consist primarily of glucocorticoids, i.v. Ig, and plasmapheresis, which result in non-specific immunosuppression (21). Furthermore, these treatments are ineffective in one third of patients (22). The demonstration in this study that CD4+ T cells are sufficient to transfer disease and that infiltrating CD4+ T cells produce IFN-γ may be more efficacious in treating neuropathy as a possible novel component of autoimmune poly-endocrinopathy-candidiasis-ectodermal dysplasia.

Disclosures

The authors have no financial conflicts of interest.

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