Coronins are evolutionarily conserved proteins that were originally analyzed as modulators of actin-dependent processes. Studies analyzing complete Coronin 1a knock-out mice have shown that this molecule is an important regulator of naive T cell homeostasis and it has been linked to immune deficiencies as well as autoimmune disorders. Nevertheless, because Coronin 1A is strongly expressed in all leukocyte subsets, it is not conclusive whether or not this phenotype is attributed to a T cell-intrinsic function of Coronin 1A. To address this research question, we have generated a T cell-specific Coronin 1a knock-out mouse (Coro1a<sup>fl/fl</sup> × Cd4<sup>[Cre]</sup>). Deletion of Coronin 1A specifically in T cells led to a strong reduction in T cell number and a shift toward the effector/memory phenotype in peripheral lymphoid organs when compared with Cd4<sup>[Cre]</sup> mice expressing wild-type Coronin 1A. In contrast to peripheral lymphoid tissue, thymocyte number and subsets were not affected by the deletion of Coronin 1a. Furthermore, T cell-specific Coronin 1a knock-out mice were largely resistant to the induction of autoimmunity when tested in the myelin oligoglycoprotein-induced EAE mouse model of multiple sclerosis. Thus, the phenotype of T cell-specific Coronin 1a deletion resembles the phenotype observed with conventional (whole body) Coronin 1a knock-out mice. In summary, our findings provide formal proof of the predominant T cell-intrinsic role of Coronin 1A.

Coronins are an evolutionarily conserved family of intracellular proteins comprising seven members in mammals. The actin-binding Coronin 1A (Coro1A) is highly expressed in all leukocytes with the exception of Kupffer cells, a liver-resident macrophage subset (for review see Ref. 1). Initially, Coro1A was identified as a factor facilitating <i>Mycobacteria tuberculosis</i> survival in macrophages through the modulation of endosomal-lysosomal fusion (2, 3). However, other macrophage functions such as phagocytosis and chemotaxis appeared normal in the absence of Coro1A expression (3, 4). Coro1A also seems to be largely dispensable for the functionality of neutrophils, mast cells, dendritic cells, and B cells, even though some controversy exists concerning the role of Coro1A in neutrophils and mast cells (5–10).

The cell type mainly affected by the germline deletion of Coro1a in mice is T cells, whereas no gross defect in other leukocyte subsets has been observed, which is somewhat surprising given the high expression of Coro1A in almost all leukocyte subpopulations. Common to all four Coro1a-deficient mouse strains, which were generated in different laboratories, are strongly reduced peripheral T cell counts (11–14). Naïve T cells are especially impaired, whereas effector/memory and regulatory T cells (Treg) are far less affected by the deletion of Coro1a. The distinct studies concurringly report that Coro1a-deficient naïve T cells show survival defects and an increased apoptosis rate. Different explanations are provided regarding the mechanism of how Coro1A regulates peripheral T cell homeostasis, including impaired signaling downstream of the T cell receptor (TCR) (12, 13, 15) and perturbed actin dynamics affecting mitochondrial membrane potential (11). In addition to impaired survival, migration defects, egress from the thymus as well as homing to the lymph nodes, have been reported to affect naïve T cell homeostasis in the absence of functional Coro1A (11, 16). In contrast to peripheral T cells, thymic development in Coro1a-deficient mice has been reported to be either normal (12) or only barely impaired, affecting merely T cell terminal differentiation and leading to reduced single positive thymocytes (11, 13).

In mice, Coro1A has been associated with resistance to autoimmunity. A nonsense mutation of Coro1a has been identified to suppress disease development in a mouse model of lupus erythematosus (15). Furthermore, Coro1a-deficient mice develop no or only mild symptoms of autoimmunity when immunized with the myelin oligoglycoprotein (MOG) peptide to induce experimental autoimmune encephalomyelitis (EAE), a common murine model of multiple sclerosis (14, 17).

MOG-induced EAE is considered a predominantly T cell-mediated disease, in which MOG-specific naïve T cells are activated and expanded during the early phase of the immune response in lymph nodes draining the immunization site. Subsequently, the differentiated effector T cells invade the central nervous system (CNS), where they initiate the recruitment of other inflammatory immune cells such as neutrophils and macrophages. Nevertheless, B cells are also discussed to contribute to the pathogenesis either by secreting autoantibodies, presenting antigens to T cells, or by suppressing effector responses. Furthermore, dendritic cells as professional antigen-presenting cells (APC) are crucial for the priming of T cells in lymphoid organs and in addition to reactivate T cells in the CNS. Thus, besides T...
cells, several different populations of immune cells may contribute to the inflammatory response leading to neuronal damage and resulting in symptoms of ascending flaccid paralysis (see Ref. 18 for a comprehensive review).

Given the abundant expression of Coro1A in many different immune cell types, the question remains of whether the phenotype of Coro1a-deficient mice can be attributed predominantly to its role in T cells. Moreover, it has not been proven that the paucity of peripheral T cells observed in conventional Coro1a-deficient mice is caused by a T cell intrinsic role of Coro1A or a lack of Coro1A expression in other leukocyte subsets. To address these points, we have generated mice lacking Coro1A expression specifically in T cells and analyzed their immune status as well as their susceptibility to the induction of EAE by immunization with the MOG peptide. Our results suggest a predominant T cell-intrinsic role of Coro1A responsible for peripheral T cell homeostasis and resistance to the development of severe EAE.

Results

Characterization of a T Cell-specific Coronin 1A Knock-out Mouse—Coro1A, which has been implicated as an important regulator of T cell functions by several studies analyzing conventional (whole body) Coro1a knock-out mice or natural mutants, is highly expressed in all leukocyte subsets (with the exception of Kupffer cells). Nevertheless, it is currently not clear whether the expression of Coro1A in T cells or other leukocyte subsets such as APCs accounts for the strong reduction of T cell counts observed with conventional knock-out mice. To address this research question, T cell-specific Coro1a knock-out mice were generated in our laboratory by crossing Coro1a"/" mice harboring loxP sites after exon 1 and 10 of the coro1a gene to Cd4-Cre transgenic mice (Tg(Cd4-cre)1Cwi/BfluJ) containing CD4 enhancer, promoter, and silencer sequences driving the expression of a Cre recombinase gene (Fig. 1A).

To determine the efficiency as well as specificity of Coro1a deletion, offspring expressing the Cre recombinase together with either a wild-type ("Cd4-Cre") or floxed version of the Coro1a gene ("Cd4-Cre × Coro1a"/"") along with conventional Coro1a knock-out mice ("Coro1a"/"") were analyzed for Coro1A protein expression. The Coro1A protein expression level in sorted CD4"/" T cells isolated from Cd4-Cre × Coro1a"/" mice was strongly reduced (to less than 10%) when compared with Cd4-Cre mice by SDS-PAGE gel and Western blotting analysis using a monoclonal antibody against Coro1A (Fig. 1B). Remarkably, as few as 1 × 10" T cells isolated from Cd4-Cre mice gave a very strong band for Coro1A on immunoblots, emphasizing that Coro1A is abundantly expressed in T cells. As expected, no Coro1A protein was detected with T cells of Coro1a"/" mice, also confirming the specificity of the monoclonal antibody, which is raised against human CORO1A but also detects its highly conserved mouse homologue.

To determine Coro1A expression on the single cell level, and thus the specificity of Coro1a deletion by the Cre recombinase in lymphocyte subsets, splenocytes of all three genotypes were analyzed by flow cytometry. Because no fluorochrome-labeled anti-Coro1A antibody was commercially available, we used the same monoclonal antibody that has been applied for immunoblotting in combination with Zenon technology (see “Experimental Procedures”). We chose this approach because it should result in less unspecific background staining than using fluorochrome-labeled secondary antibodies. The results with splenocytes from Coro1a"/" mice, showing negligible “false Coro1A-positive” CD4" T cells, and a clear positive population with
**T Cell-specific Knock-out of Coronin 1A**

Additional flow cytometric analyses of the peripheral T cell compartment revealed that especially the CD4<sup>+</sup> T cell compartment was affected by deletion of *Coro1a*, leading to a reduced percentage of CD4<sup>+</sup> T cells in both knock-out lines (Fig. 3B). Interestingly, whereas the percentage of CD4<sup>+</sup> T cells was not significantly different between germline and T cell-specific *Coro1a* deletion, the frequency of CD8<sup>+</sup> T cells was increased in the spleen of conventional but not of T cell-specific *Coro1a* knock-out mice. This difference between both *Coro1a* knock-out lines in regard to CD4<sup>+</sup> and CD8<sup>+</sup> cell frequency is further illustrated by the significantly lower CD4:CD8 ratio in the spleen of conventional *Coro1a* knock-out mice.

As mentioned above, the main subset affected by *Coro1a* deletion seems to be naïve CD4<sup>+</sup> T cells. Therefore, this subset was analyzed by flow cytometry using CD62L and CD44 to distinguish naïve and effector/memory T cells. T cell-specific deletion of *Coro1a* resulted in a strong reduction of naïve CD4<sup>+</sup> T cells and induced a shift toward an effector/memory phenotype. However, these changes were less pronounced than observed for CD4<sup>+</sup> T cells from conventional *Coro1a* knock-out mice (Fig. 4).

**Deletion of Coro1a in T Cells Protects from the Development of EAE**—The most striking phenotype of conventional *Coro1a* knock-out mice was their resistance to EAE induction using the MOG(35–55) peptide-based protocol (14, 17). Given the similar phenotype of mice harboring either T cell-specific or germ-line deletion of *Coro1a*, we expected that deletion of *Coro1a* in T cells would also confer protection in this model of autoimmunity. This was indeed observed when the three genotypes were immunized with the MOG(35–55) peptide and disease progression was monitored: mice lacking *Coro1a* only in T cells were as well protected as mice lacking *Coro1a* in all their cells (Fig. 5). In summary, our results show a predominant T cell intrinsic role of Coro1A with regard to T cell function.

**Discussion**

Several studies have associated mutations in the *Coro1a* gene with resistance to autoimmunity. A nonsense mutation that had arisen spontaneously has been identified as a disease-sup-
pressing allele in lupus-prone Faslpr mice (15). This point mutation introduces a stop codon in the middle of the protein, leading to a truncated version of Coro1A, which fails to localize to the plasma membrane. Furthermore, conventional Coro1A-deficient mice, generated independently in distinct laboratories, were protected against the development of severe signs of EAE induced by immunization with the MOG peptide (14, 17). This phenotype has been attributed to alterations of intrinsic T cell function, namely impaired migration, cell activation, and survival. Of note, however, those mouse strains lack functional Coro1A in all their cells. Our results obtained with mice lacking Coro1A specifically in T cells support the notion of a predominant T cell intrinsic role of Coro1A underlying the resistance to autoimmunity. Thus, similarly to conventional Coro1A-deficient mice, Cd4-Cre x Coro1a<sup>fl/fl</sup> mice show strongly reduced peripheral CD4<sup>+</sup> and CD8<sup>+</sup> T cell counts and are largely protected from the induction of EAE.

Before conditional Coro1A-deficient mice were generated, the conclusion that T cell intrinsic Coro1A accounts for reduced susceptibility of autoimmunity was drawn mainly from transfer experiments. On one hand, the transfer of T cells bar-
ing the point mutation described above was sufficient to reduce lupus-like diseases (15). On the other hand, the transfer of wild-
type CD4<sup>+</sup> T cells before immunization did restore the suscep-
tibility of Coro1A-deficient mice to EAE induction (17). The later experimental approach suggests that Coro1A-deficient APCs are fully capable of priming T cells and promoting effec-
tor T cell differentiation as long as those T cells express Coro1A. The assumption that Coro1A is dispensable for antigen presentation and T cell activation by APCs is further supported by the observation that bone marrow-derived dendritic cells induce antigen-specific T cell proliferation regardless of Coro1A expression (8). Thus, it seems that Coro1A expression in T cells rather than in APCs is essential for the activation of autoantigen-specific T cells and the development of symptoms of EAE. This is in accordance with our results of T cell-specific Coro1A-deficient mice being largely resistant to EAE induction.
It is believed that myelin-specific T cells, which have escaped central tolerance, are present in the peripheral T cell pool in a state of ignorance (19) and, in addition, their activation is prevented by Tregs (17, 20–22). Therefore, the balance between distinct T cell subsets may dictate disease outcome after immunization with myelin-derived peptides. In this regard, it is worth noting that an increased Treg/naive T cell ratio was observed in the absence of Cos1a, in conditional as well as T cell-specific knock-out mice (see Ref. 17; data not shown). However, whereas the transfer of wild-type CD4+ T cells did impact on EAE development, the depletion of CD25+ Tregs did not restore disease susceptibility (17), indicating that resistance to EAE in the absence of Cos1a is most likely caused by disturbed naive T cell priming.

Unexpectedly, considering the decreased EAE symptoms upon primary immunization with the MOG peptide, Cos1a-deficient mice not only overcome the defect observed during initial induction, but also demonstrate hypersusceptibility upon the reinduction of EAE (14). The authors explain this phenotype by defective SMAD3-mediated TGFβ receptor signaling, resulting in enhanced interferon-γ and interleukin-17 production when T cells lack Cos1a. These findings are consistent with the observation that Cos1a-deficient T cells are fully competent to express Th1, Th2, and Th17 effector cytokines upon polyclonal stimulation with antibodies recognizing CD3 and CD28 (17). Therefore, a decreased disease severity in the absence of Cos1A expression cannot be attributed to a general defect of effector T cell differentiation, but might rather be caused by the reduced overall CD4+ T cell number. One could further speculate that there are too few MOG-specific T cells to act as pioneer cells and to induce disease (23); however, the threshold number of effector T cells needed for substantial inflammatory response might be reached after expansion following immunization. The conclusion that the major defect lies in the naive T cell compartment while effector/memory T cells are functional is supported by a study analyzing Cos1a-deficient mice in a model of concanavalin A-induced liver injury, which showed a similar inflammation score for wild-type and knock-out mice (24). The response to intravenous concanavalin A occurs within a few hours after intravenous administration and it is therefore very unlikely that naive T cells are responsible for acute liver injury in this model. One could speculate that the different dependence of naive and effector/memory T cells on Cos1A is due to different requirements of TCR signal strength for their activation, which would be consistent with the role of Cos1A in signaling downstream of the TCR (12, 13, 15, 16, 25). Of note, the paucity of naive T cells in T cell-specific Cos1a-deficient mice was not as strong as in conventional knock-out mice. This finding suggests that naive T cell homeostasis, at least to some extent, also depends on Cos1A expression in non-T cells. However, another explanation could be some degree of residual expression of Cos1A in naive T cells of Cos4-Cre × Cos1afl/fl mice.

An important role of Cos1A for an intact immune system has also been described for humans. Intriguingly, similar to the murine system, all 7 COS1A-deficient patients reported to date have severe T cell lymphocytopenia, whereas B cells and natural killer cells were present in normal to low numbers (26–31). Those reports emphasize the importance of Cos1A for T cell homeostasis not only in mice but also in humans. Common to all patients were recurrent respiratory infections and the inability to control Epstein-Barr virus, associated with lymphoma at a young age. In this regard, Cos1a-deficient mice were highly susceptible to vesicular stomatitis virus, most likely due to the delayed production of neutralizing antibodies, which requires CD4+ T cell help (32). Interestingly, lymphocytic cho- riomeningitis virus clearance, which depends on CD8+ T cells, was comparable with wild-type mice, suggesting a different requirement for Cos1A in CD8+ versus CD4+ function. Moreover, in the current study we observed a shift toward a lower CD4:CD8 ratio in the absence of Cos1A, which was more pronounced in conventional than conditional Cos1a-deficient mice. This difference might be attributed to the slightly less efficient deletion of Cos1A expression in CD8+ than CD4+ T cells.

Besides its primary expression in the hematopoietic lineage, Cos1A was also detected in neuronal tissue (33, 34). However, based on our data obtained with T cell-specific Cos1A-deficient mice, we exclude that neuronal Cos1A plays any role in neuronal pathology and axonal injury, which was not very likely. Furthermore, in both mice and humans, a lack of functional Cos1A causes severe neurobehavioral defects, including social deficits, increased aggression, and learning disabilities (26, 33). We observed that, in contrast to conventional Cos1a-deficient mice, Cd4-cre × coro1afl/fl mice did not display enhanced aggression, which is consistent with the specific absence of Cos1A from T cells (data not shown). Taken together, our results demonstrate a crucial T cell-intrinsic role of Cos1A in the development of EAE.

**Experimental Procedures**

**Mice**—Coron1a-deficient mice (Cos1a−/−) were generated using Cre/LoxP-mediated deletion as described previously by Kaminski et al. (14). To obtain mice harboring a T cell-
specific knock-out of Coro1a, the same floxed Coro1a mouse line was crossed in our laboratory to Cd4-Cre transgenic mice (Tg(Cd4-cre)1Cwi/Bflu) purchased from Charles River Laboratories. The corresponding littermates (Cd4-cre × Coro1a^floxed/flox and Cd4-cre) were bred in-house as separate lines homozygous for the floxed Coro1a allele and heterozygous for the Cd4-cre transgene. All mouse lines were maintained under specific pathogen-free conditions. Animal experiments were conducted in accordance with the Austrian Animal Welfare Law and Animal Experimental Act (BGBl number 501/1988 and BGBl number 114/2012), and were approved by the Committee of the Animal Care of the Austrian Federal Ministry of Science and Research (BM:WF/66.011/0064-WF/3b/2016). Genotyping was performed by PCR following the protocol published on the JAX homepage (for Cd4-Cre) or using the following primers and thermocycler settings: ggtcctcagtagctgactg (forward), tagca-gaaccgccagg (reverse); 35 cycles of 95 °C for 30 s, 55 °C for 45 s, and 72 °C for 1 min. The expected PCR product size is 140 bp for wild-type Coro1a and 250 bp for the floxed Coro1a allele.

**Thymocyte and Splenocyte Isolation and T Cell Sort**—Single cell suspensions of spleens and thymi were prepared by mechanical disintegration using metal sieves and cell strainers (Falcon), followed by the removal of erythrocytes by lyses (Mouse Erythrocyte Lysing Kit, R&D Systems). After a washing step with PBS, 0.5% BSA, 2x ml EDTA (viable), cell counts were determined with a LUNA Automated Cell Counter (Logos Biosystems). CD4^+ and CD8^+ cells were positively selected using a mix of CD4 (L3T4) and CD8a (Ly-2) MicroBeads together with LS columns and a QuadroMACS Separator (all Miltenyi Biotec) according to the manufacturer’s instructions. Sort purity was checked by flow cytometry.

**SDS-PAGE and Immunoblotting**—Cell lysates from splenocytes were prepared and subjected together with precision plus protein standard (Bio-Rad) to SDS-gel electrophoresis and immunoblotting as described previously (35). Unspecific binding was blocked with 5% nonfat milk powder. Monoclonal antibodies detecting Coronin 1A (sc-100925) or Fyn (sc-16) were purchased from Santa Cruz Biotechnology. HRP-conjugated secondary antibodies against mouse and rabbit IgG were purchased from Thermo Scientific. For detection, SuperSignal West Pico Chemiluminescent Substrate (Thermo Scientific) was used and the bands were visualized using hyperfilm (Amer sham Biosciences) and SuperFx Enviro Safe 25 together with Roentrol Enviro Safe AC (Tental). Quantification was performed using the ImageJ software.

**Flow Cytometry**—Surface staining, including preincubation with FcR block; anti-CD16/32 (BD Biosciences), was performed as described previously (17). The following antibodies were used: anti-CD4 PE, anti-CD3 PECy7, anti-CD8 PerCP Cy5.5, anti-CD62L APC, and anti-CD4 bv605 (all from Biolegend).

Intracellular Coro1A was stained using a mouse monoclonal anti-Coro1A antibody (Santa Cruz Biotechnology) together with the Zenon Alexa 488 mouse IgG2a Labeling Kit (Thermo Fisher Scientific) after the cells had been stained for surface antigens and subsequently fixed and permeabilized using fixation buffer and intracellular staining permeabilization wash buffer obtained from Biolegend. The samples were subjected to an additional poststaining fixation step with 2% paraformaldehyde for 20 min at room temperature. Data were acquired on a FACScalibur (CellQuest) or Fortessa (DivA) instrument (both BD Biosciences) and analyzed with FlowLogic software (eBioscience).

**Induction of Active EAE**—EAE was induced by active immunization with the MOG(35–55) peptide based on established protocols (35). To that end, the 9–13-week-old mice were immunized subcutaneously in the back on day 0 with 400 μg of MOG(35–55) peptide (NeoSystems, Strasbourg, France) emulsified in 100 μl of complete Freund’s adjuvant (Thermo Scientific) at a final volume of 200 μl in PBS. On days 0 and 2, the animals were injected with 400 ng of pertussis toxin (Sigma) in 100 μl of intraperitoneal PBS. Clinical signs of EAE were assessed daily according to the standard scoring protocol as published (17).

**Statistical Analysis**—The data are presented as single values plus the mean or represent the mean ± S.E.; FACS dot plots and EAE disease scores are shown as representative results (indicated in the figure legends). The number of mice (n) used per experiment and the number of experiments performed are listed in each figure legend. The data were analyzed for statistical significance by one- or two-way ANOVA with the Bonferroni post hoc test using GraphPad Prism software (GraphPad Software Inc.) as indicated in the figure legends.

**Author Contributions**—K. S. designed, performed, and analyzed the experiments and wrote the manuscript. G. B. conceived and coordinated the study. V. K. and N. H. K. performed the experiments shown in Fig. 5. All authors reviewed the results and approved the final version of the manuscript.

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