ranging from 1 (not at all important) to 7 (extremely important). The importance assigned to competence was significantly higher than the importance assigned to any of the other 12 traits ($Ps < 0.005$).
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14. In the studies involving these races, we used photographs of the Democratic and Republican candidates (*12*).
15. In addition, the accuracy of the predictions was not affected by the race and sex of the candidates. This is important because participants might have used race and sex stereotypes to make competence judgments for contests in which the candidates were of different sexes and races. For example, in such contests Caucasian male candidates were more likely to win. However, if anything, competence judgments predicted the outcomes of elections in which the candidates were of the same sex and race (73.1% for the Senate and 68.5% for the House) more accurately than elections in which they were of different sexes and races (67.9% and 64.3%, respectively). This difference possibly reflects participants' social desirability concerns when judging people of different race and sex.
16. For races with more than two candidates, we standardized this difference so that it was comparable to the difference in races with two candidates. Specifically, the difference between the votes of the winner and those of the runner-up was divided by the sum of their votes.
17. From the scatterplot showing the relation between competence judgments and votes for Senate (Fig. 1B), seven races (three in the lower right quadrant and four in the upper left quadrant) could be identified as deviating from the linear trend. It is a well-known fact that incumbents have an advantage in U.S. elections (*18*). In six of the seven races, the incumbent won but was judged as less competent. In the seventh race (Illinois, 2004) there was no incumbent, but the person who won, Barack Obama, was the favorite long before the election. Excluding these seven races, the correlation between competence judgments and differences in votes increased to 0.64 ($P < 0.001$). Although incumbent status seemed to affect the strength of the linear relation between inferences of competence and the margin of victory, it did not affect the prediction of the outcome. Competence judgments predicted the outcome in 72.9% of the races in which the incumbent won, in 66.7% of the races in which the incumbent lost, and in 68.8% of the cases in which there was no incumbent ($\chi^2 < 1.0$ for the difference between these percentages; $P = 0.89$).
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19. A bootstrapping data simulation showed that increasing the sample size to more than 40 participants does not improve the accuracy of prediction substantially (*12*) (fig. S1).
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27. For these studies, we used the 2000 and 2002 Senate races (*12*).
28. An additional analysis from a study in which participants made judgments of the candidates for the Senate (2000 and 2002) on 13 different traits [see (*10*) for the list of traits] provided additional evidence that inferences of competence were the key determinants of voting preferences in this situation. We regressed voting preferences on the 13 trait judgments. The only significant predictor of these preferences was the judgment of competence [$\beta = 0.67$, $t(49) = 4.46$, $P < 0.001$].
29. A similar finding was obtained in an early study conducted in Australia (*30*). Hypothetical votes based on newspaper photographs of 11 politicians were closely related to the actual votes in a local government election. Moreover, both hypothetical and actual votes correlated with inferences of competence.
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34. There is some evidence that judgments of intelligence from facial appearance correlate modestly with IQ scores (*35*). However, these correlations tend to be small [e.g., <0.18 in (*35*)], they seem to be limited to judgments of people from specific age groups (e.g., puberty), and the correlation is accounted for by the judges' reliance on physical attractiveness. That is, attractive people are perceived as more intelligent, and physical attractiveness is modestly correlated with IQ scores.
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Supporting Online Material

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TLR11 Activation of Dendritic Cells by a Protozoan Profilin-Like Protein

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Mammalian Toll-like receptors (TLRs) play an important role in the innate recognition of pathogens by dendritic cells (DCs). Although TLRs are clearly involved in the detection of bacteria and viruses, relatively little is known about their function in the innate response to eukaryotic microorganisms. Here we identify a profilin-like molecule from the protozoan parasite *Toxoplasma gondii* that generates a potent interleukin-12 (IL-12) response in murine DCs that is dependent on myeloid differentiation factor 88. *T. gondii* profilin activates DCs through TLR11 and is the first chemically defined ligand for this TLR. Moreover, TLR11 is required in vivo for parasite-induced IL-12 production and optimal resistance to infection, thereby establishing a role for the receptor in host recognition of protozoan pathogens.

Mammalian Toll-like receptors (TLRs) play a fundamental role in the initiation of immune responses to infectious agents through their recognition of conserved microbial molecular patterns (*1*). TLR signaling in antigen-presenting cells, such as dendritic cells (DCs), results in the production of cytokines and costimulatory molecules that are required for initiation of the adaptive immune response (*2*, *3*). Human and mouse TLR family members have been shown to have distinct ligand specificities, recognizing molecular structures such as lipopeptide (TLR2) (*4*), lipopolysaccharide (TLR4) (*5*, *6*), flagellin (TLR5) (*7*), double- and single-stranded RNA (TLR3 and TLR7) (*8*–*11*), and CpG motifs of DNA (TLR9) (*12*). Although several TLRs have been shown to be important for immune responses to microbial products in vitro, their role in host resistance to infection appears to be complex and not

readily attributed to the function of a single TLR (*13*). Of particular help in assessing the role of TLR functions has been a mouse carrying a deletion in the gene encoding myeloid differentiation factor 88 (MyD88), an adaptor molecule that is essential for most TLR, interleukin-1 (IL-1), and IL-18 signaling (*14*). MyD88$^{-/-}$ mice have been shown to be acutely susceptible to a wide variety of bacterial, fungal, protozoan, and viral agents (*13*).

A critical host mediator produced in response to TLR activation is IL-12. This cytokine is synthesized by DCs, macrophages, and neutrophils and plays a pivotal role in the production of interferon-γ (IFN-γ), which in turn activates antimicrobial effector cells (*15*). In previous studies, we have shown that IL-12 is essential for host resistance to the protozoan parasite *Toxoplasma gondii* and that DCs produce large quantities of the cytokine in response to stimulation with this pathogen (*16*, *17*). Both host resistance to *T. gondii* and parasite-induced IL-12 production by DCs have been shown to require MyD88, which strongly suggests the involvement of TLR signaling (*18*). Nevertheless, the question of which TLR molecule or molecules govern *T. gondii*–induced IL-12 production by DCs remained unanswered.

In addition to MyD88 signaling, activation of DCs by *T. gondii* has been shown to involve ligation of the chemokine receptor CCR5 by a *T. gondii* protein, cyclophilin-18 (C-18) (*19*, *20*). Because stimulation by C-18 does not explain the MyD88 dependence of the IL-12 response to the parasite, we searched for an additional ligand in *T. gondii* that might trigger DC IL-12 production by a MyD88-dependent but CCR5-independent pathway.

We used DCs from CCR5-deficient mice as responder cells in purifying an IL-12–inducing fraction from STAg, a soluble extract of the tachyzoite stage of the parasite (*17*). Pilot studies indicated that the cytokine-stimulating activity was protease-sensitive (fig. S1A), and we therefore fractionated STAg by gel filtration (Fig. 1A). A low-molecular-weight peak consisting of the two most active fractions (B7 and B8) was further separated, yielding a single fraction (fig. S1B) that stimulated high levels of IL-12 production and contained a single silver-stained band on SDS–polyacrylamide gel electrophoresis (SDS-PAGE) (Fig. 1B), which was analyzed by mass spectrometry, followed by Sequest peptide mapping (fig. S1C). A high-scoring match was found for a tryptic peptide in the *T. gondii* clustered expressed sequence tag (EST) database (http://ToxoDB.org). Based on its complete sequence, the *T. gondii* protein identified by us has a predicted molecular mass of 17.5 kD and contains consensus motifs shared by profilins, a class of actin-binding proteins (*21*). Database searches performed with the *T. gondii* profilin (PFTG) sequence revealed significant homology only with profilin genes that are present in other apicomplexan protozoa (Fig. 1C and figs. S2 and S3).

The cloned *T. gondii* profilin-like gene was used to transform *Escherichia coli*, and

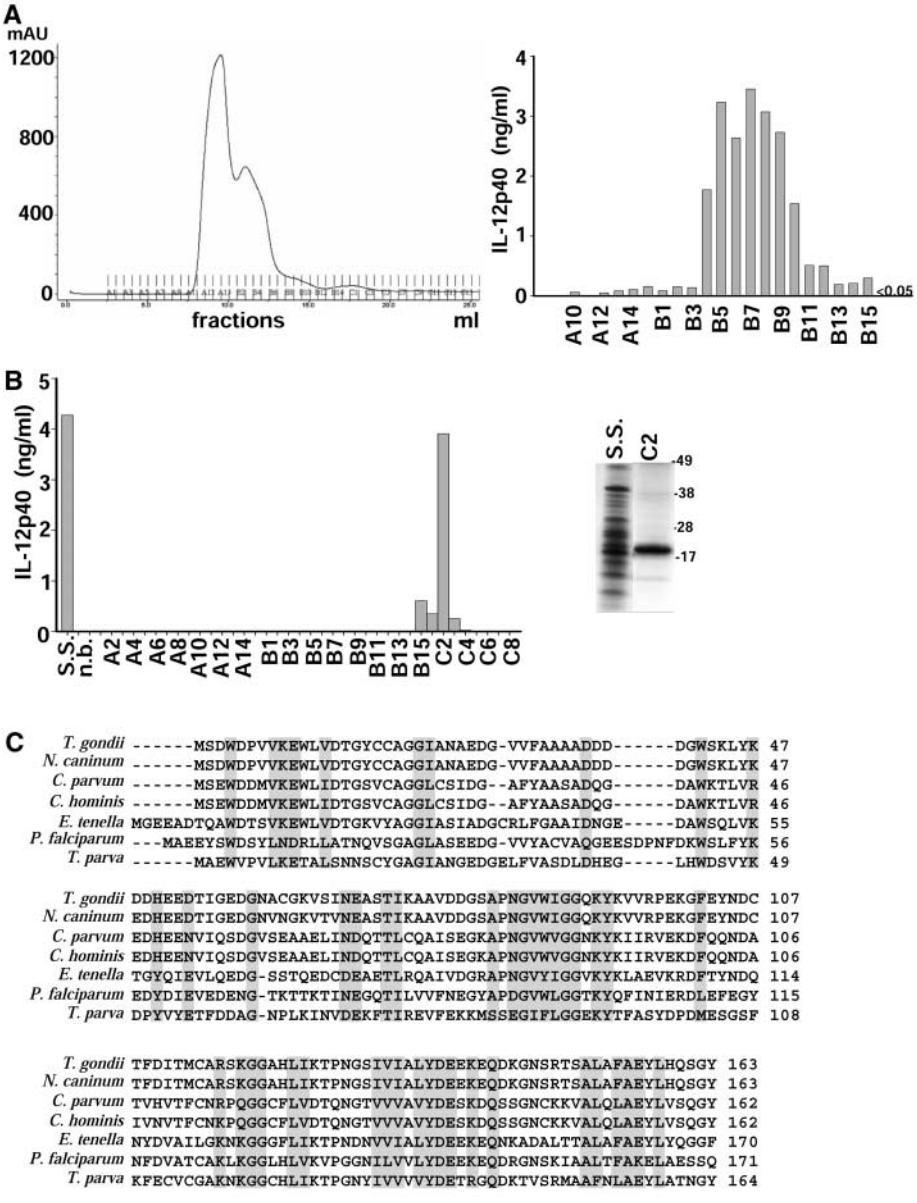

Fig. 1. Isolation of a major IL-12–inducing protein from *T. gondii*. (**A**) Initial separation of soluble tachyzoite extract (STAg) on Superdex-75 Sepharose and assay of individual fractions for their ability to stimulate IL-12 production by splenic DCs from CCR5$^{-/-}$ mice. mAU, relative milliabsorbance at 280 nm. (**B**) Further purification by Mono Q anion-exchange chromatography of fractions B7 and B8 from the first separation. The inset at right shows a silver-stained SDS-PAGE analysis of the fraction (C2) with peak IL-12–inducing activity compared with the starting sample (S.S.). (**C**) Amino acid sequence alignment of the cloned *T. gondii* IL-12–inducing protein with its nearest homologs in the National Center for Biotechnology Information database. All these sequences are profilin-like proteins from the related apicomplexan parasites *Neospora caninum* (93% homology), *Cryptosporidium parvum* (63% homology), *Cryptosporidium hominis* (63% homology), *Eimeria tenella* (67% homology), *Plasmodium falciparum* (58% homology), and *Theileria parva* (53% homology).

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the resulting lysate induced IL-12 production by DCs at approximately 20 times the level seen with controls (fig. S4A). The purified PFTG recombinant protein induced potent IL-12 p40 and IL-12 p70 responses from splenic DCs and was approximately 100 times more active in a dose-response analysis than unfractionated STAg (Fig. 2). In contrast, recombinant C-18 was found to be less active than STAg in inducing IL-12 production (*20*, *22*).

T. gondii is known to preferentially induce IL-12 production in CD8α$^+$ DCs (*17*), and a similar DC subset restriction was observed for IL-12 (Fig. 2 and fig. S4B), tumor necrosis factor (TNF), and IL-6 induction by PFTG (fig. S4C). Consistent with the known MyD88 dependence of *T. gondii*–induced cytokine production (*18*), DCs from MyD88$^{-/-}$ mice displayed severely impaired IL-12, TNF, and IL-6 responses to PFTG (Fig. 2 and fig. S4, B and C).

Two distinct TLRs have been implicated in the recognition of protein ligands. TLR5 has been shown to be triggered by bacterial flagellin, whereas TLR11 signaling is stimulated by protease-sensitive molecules in uropathogenic bacteria (*7*, *23*). We observed that TLR11 but not TLR5 transfectants displayed dose-dependent nuclear factor κB (NF-κB) activation when stimulated with PFTG (Fig. 3A). We next compared the response to PFTG and STAg stimulation of splenic DCs from TLR11$^{-/-}$ mice with the response of DCs from other TLR-deficient mice. Unlike DCs from wild-type animals, TLR11$^{-/-}$ DCs failed to produce IL-12p40 (Fig. 3B), TNF, or IL-6 (*22*) in response to either PFTG or STAg at doses as high as 1 μg/ml, whereas no significant defects in cytokine response were observed with comparable DC populations from TLR2- (*4*), TLR3- (*8*), TLR4- (*6*), TLR7- (*24*), or TLR9-deficient (*12*) mice (fig. S5A) (*22*). Fluorescence-activated cell sorter analysis confirmed that the defective response observed with the TLR11$^{-/-}$ cell population was not the result of a deficiency in CD8α$^+$CD11c$^+$ DCs (fig. S5B). TLR11 mRNA was detected in both CD8α$^+$ and CD8α$^-$ DCs, although at higher levels in the former subpopulation (fig. S5C).

To investigate whether the PFTG-TLR11 interaction was also critical for IL-12 induction in vivo, wild-type and TLR11$^{-/-}$ mice were injected with STAg or PFTG and examined for serum cytokine levels. In contrast to the control animals, which produced a vigorous IL-12 response, TLR11$^{-/-}$ mice failed to produce detectable levels of the cytokine (Fig. 4A). Moreover, splenic DCs in STAg- or PFTG-injected TLR11$^{-/-}$ mice as well as MyD88$^{-/-}$ mice failed to migrate into T cell areas (Fig. 4B) or stain with monoclonal antibody to IL-12 (*22*), which is the response typically seen in wild-type animals (*17*). Finally, to test whether TLR11 also governs IL-12–dependent host resistance to live parasite infection, control and TLR11$^{-/-}$ mice were infected with ME-49, an avirulent *T. gondii* strain. In contrast to infected wild-type animals, which produced high levels of circulating IL-12p40 and IFN-γ, *T. gondii*–exposed TLR11$^{-/-}$ mice displayed low serum IL-12 levels, which were only slightly elevated above those seen in MyD88$^{-/-}$ animals, as well as reduced levels of IFN-γ (Fig. 4C). Nevertheless, in contrast to MyD88$^{-/-}$ animals, the infected TLR11$^{-/-}$ mice survived the acute phase of infection. However, the TLR11$^{-/-}$ mice clearly showed impaired resistance, as was made evident by a nearly fivefold elevation in the numbers of brain tissue cysts relative to wild-type animals measured during the chronic phase of infection (Fig. 4D).

The results presented here identify the first chemically defined ligand for TLR11 and demonstrate previously unappreciated roles for TLR11 signaling in pathogen-induced cytokine production by DCs, as well as host resistance to protozoan infection. The initial observation that proteinase K digestion destroys the ability of uropathogenic *E. coli* lysates to stimulate TLR11 had suggested that this receptor recognizes proteins (*23*). Our findings confirm this hypothesis by demonstrating direct TLR11 stimulation by a recombinant parasite protein. Although studies are in progress to determine whether structurally related ligands also exist in uropathogenic bacteria, *T. gondii* profilin homologs are clearly present in other apicomplexan parasites (Fig. 1C and figs. S2 and S3). In this regard, we have found that recombinant profilins from *Cryptosporidium parvum* and *Plasmodium falciparum* induce IL-12 production in varying degrees (fig. S6), and a profilin cloned from *Eimeria tenella* was recently

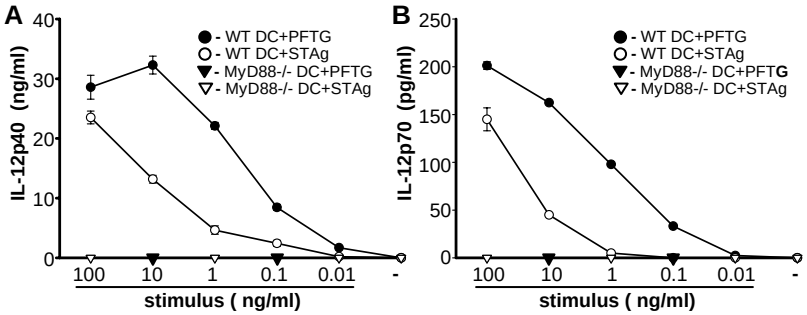

Fig. 2. Dose response of wild-type versus MyD88$^{-/-}$ DCs to PFTG in comparison with the response to unfractionated STAg. Sort-purified CD8α$^+$CD11c$^+$ splenic DCs from either C57BL/6 or MyD88$^{-/-}$ mice were exposed to graded doses of recombinant PFTG or STAg, and IL-12p40 (**A**) and IL-12p70 (**B**) were measured in supernatants after overnight culture. The data shown are the mean ± SD of triplicate assays performed at each dilution and are representative of four experiments performed.

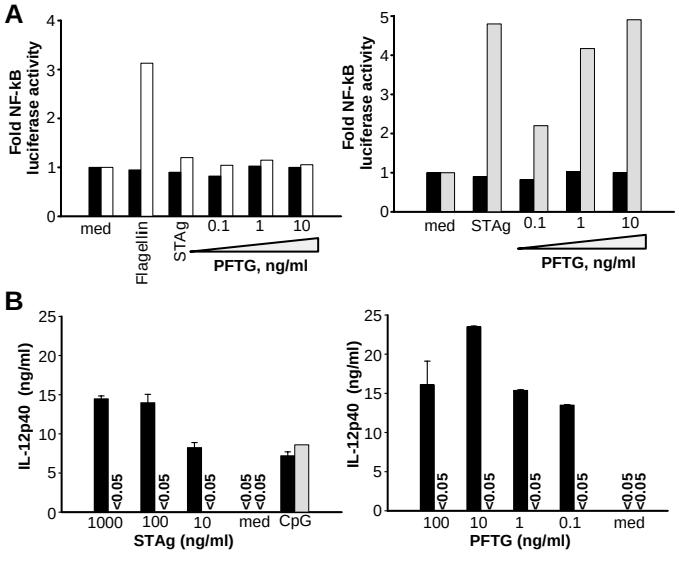

Fig. 3. PFTG is a TLR11 ligand. (**A**) PFTG stimulates TLR11- but not TLR5-transfected cells. CHO-K1 cells transfected with empty vector (black bars), TLR5-expressing vector (white bars, left panel), or TLR11-expressing vector (gray bars, right panel) were stimulated with increasing concentrations of recombinant PFTG, STAg (1 μg/ml), flagellin C (1 μg/ml, InvivoGen), or left untreated in medium (med), and NF-κB luciferase activity was measured 4 hours later. The data shown are means of duplicate points from a representative experiment out of two performed. (**B**) TLR11 is required for the IL-12 response of DCs to both PFTG and STAg. Total splenic DCs from wild-type (black bars) or TLR11$^{-/-}$ (gray bars) mice were exposed to graded doses of either STAg, PFTG, or CpG (10 μM), and IL-12p40 production was measured after overnight incubation. The data shown are the mean ± SD of triplicate assays performed at each dilution and are representative of three experiments performed (<0.05 = below the limit of detection).

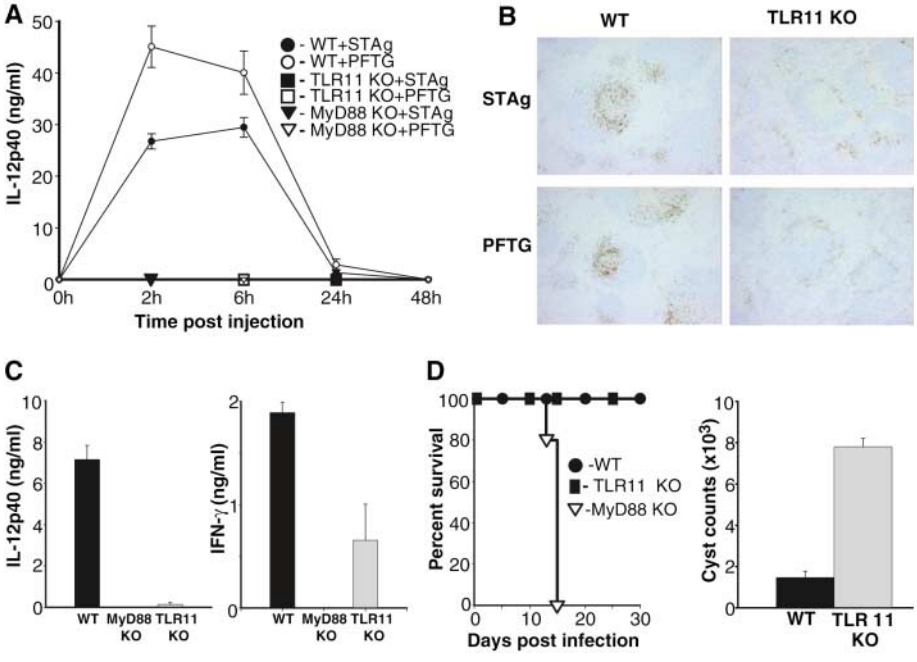

Fig. 4. TLR11 plays a major role in the in vivo IL-12 response to STAg and PFTG as well as to infection with live *T. gondii*. (**A**) TLR11 is required for IL-12 production in response to injected STAg or PFTG. TLR11 knockout (KO), littermate controls, and MyD88 KO mice (n = 3 or 4 per group) were injected intraperitoneally with 10 μg of STAg or recombinant PFTG and were bled at the time points indicated. The data shown are the group means ± SD from duplicate IL-12p40 enzyme-linked immunosorbent assay (ELISA) measurements performed on each mouse. (**B**) TLR11 is required for the migration of splenic DCs induced by STAg or PFTG. TLR11$^{-/-}$ or wild-type (WT) animals were injected with STAg or PFTG as described above, and spleens were removed 6 hours later for immunocytochemistry. The brown stain indicates CD11c^{+} cells, whereas the blue stain marks B220^{+} cells to localize B cell areas in the spleen. The images shown are representative of multiple sections examined in three or four mice per group. Sections from injected MyD88$^{-/-}$ mice were indistinguishable from those from TLR11$^{-/-}$ mice (*22*). (**C**) TLR11$^{-/-}$ mice infected with an avirulent strain of *T. gondii* display deficient IL-12 and IFN-γ production. C57BL/6, MyD88$^{-/-}$, and TLR11$^{-/-}$ mice (five animals per group) were infected with an average of 20 cysts per mouse of the ME49 strain of *T. gondii*, and serum IL-12p40 and IFN-γ responses were measured 5 days later by ELISA. The data shown are pooled from two individual experiments that gave comparable results. (**D**) Cumulative survival of the mice shown in (C). All surviving animals were killed on day 30 and brain cysts counts were determined as a measure of infection level. The cyst numbers shown are the pooled means ± SD from the two experiments performed.

shown to have similar activity (*25*). Together these findings suggest that TLR11 may broadly recognize apicomplexan profilins.

Host resistance to *T. gondii* in mice has previously been shown to depend on both MyD88 and IL-12 production, and DCs are a major source of this cytokine (*16*–*18*). The data presented here establish TLR11 as the major pattern recognition receptor involved in the triggering of DC IL-12 production by *T. gondii* and identify the first parasite-derived protein TLR ligand. Although DC IL-12 production appeared to be almost totally impaired in infected TLR11$^{-/-}$ mice, these animals, unlike either MyD88$^{-/-}$ or IL-12$^{-/-}$ mice (*18*), retained partial resistance to challenge and survived the acute phase of the infection, most likely because of a residual IFN-γ response. This unexpected resistance may reflect the contribution of other MyD88-dependent IL-1/TLR family members (*13*) functioning together with the small amount of IL-12 still produced in the infected TLR11$^{-/-}$ mice. In this regard, it is of interest that TLR2$^{-/-}$ mice show increased susceptibility to *T. gondii* infection, but only when abnormally high challenge doses are used (*26*).

Rodents are important intermediate hosts in the natural life cycle of *T. gondii*, and although it causes disease in humans, the parasite is also a major pathogen of livestock. Although our results establish a role for TLR11 in the response of mice to *T. gondii*, human TLR11 is nonfunctional because of the presence of a stop codon in the gene (*23*). At present, it is not clear whether TLR11 recognition of *T. gondii* is of importance in limiting infection in other mammalian species or whether humans use alternative pattern recognition receptors in the innate response to *T. gondii*.

The *T. gondii* profilin-like molecule described here is the second known microbial protein recognized by a TLR, the first being flagellin, the ligand for TLR5 (*7*). Flagellin is required for bacterial motility, and the region of the molecule involved in TLR5 interaction is highly conserved and necessary for this function (*27*). Profilin-like molecules structurally related to PFTG are present in a number of apicomplexan protozoa. Although their exact cellular functions have not been established, their predicted actin-binding activity suggests that, like flagellin, they may be involved in parasite motility and/or invasion (*28*). Studies are in progress to both define the structural domain in PFTG that is necessary for TLR11 interaction and to determine whether it is phylogenetically conserved among related protozoa and therefore serves as a pathogen-associated molecular pattern for this group of eukaryotes.

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Supporting Online Material

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