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TGF2 Negatively Regulates Type 1 Immunity against *Toxoplasma gondii*

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IL-12–mediated type 1 inflammation confers host protection against the parasitic protozoan *Toxoplasma gondii*. However, production of IFN-γ, another type 1 inflammatory cytokine, also drives lethality from excessive injury to the intestinal epithelium. As mechanisms that restore epithelial barrier function following infection remain poorly understood, this study investigated the role of TGF2 (TFF2), a well-established regulator of mucosal tissue repair. Paradoxically, TFF2 antagonized IL-12 release from dendritic cells (DCs) and macrophages, which protected TGF2-deficient (TFF2−/−) mice from *T. gondii* pathogenesis. Dysregulated intestinal homeostasis in naive TFF2−/− mice correlated with increased IL-12/23p40 levels and enhanced T cell recruitment at baseline. Infected TFF2−/− mice displayed low rates of parasite replication and reduced gut immunopathology, whereas wild-type (WT) mice experienced disseminated infection and lethal ileitis. p38 MAPK activation and IL-12p70 production was more robust from TFF2−/−CD8+ DC compared with WT CD8+ DC and treatment of WT DC with rTFF2 suppressed TLR-induced IL-12/23p40 production. Neutralization of IFN-γ and IL-12 in TFF2−/− animals abrogated resistance shown by enhanced parasite replication and infection-induced morbidity. Hence, TFF2 regulated intestinal barrier function and type 1 cytokine release from myeloid phagocytes, which dictated the outcome of oral *T. gondii* infection in mice. *The Journal of Immunology*, 2012, 189: 000–000.

*Toxoplasma gondii* is an obligate intracellular protozoan that, upon peroral infection, rapidly crosses the gastrointestinal epithelium and disseminates through lymphatic, hepatic, and nervous tissues (1, 2). Host-mediated control of parasite replication is dependent on the production of IL-12 and IFN-γ from myeloid and lymphoid lineages, respectively (3–6). Oral inoculation of C57BL/6 mice with *T. gondii* tissue cysts causes severe inflammatory bowel disease (IBD), characterized by weight loss, massive granulocytic inflammation, excessive production of Th1-associated cytokines, epithelial invasion of enteric microbes, and mortality within 9–15 d (1, 7). TLR activation and excessive inflammatory cytokine release are considered to drive the epithelial cell injury that results from *T. gondii* infection in C57BL/6 mice (8), but the pathogenesis of oral toxoplasmosis remains poorly understood.

Trefoil factor (TFF)2 is one of three “trefoil-motif” containing proteins (TFF1–3) that promotes restitution, the rapid and directed movement of epithelia to cover exposed areas of basement membrane tissue following mucosal insult (9, 10). The predominant sources of TFF2 are stromal cells (epithelia, endothelia, and fibroblasts), but TFF2 mRNA transcripts are also expressed by tissue macrophages (10, 11). Although TFF2 and TFF3 can both down-regulate gastric and colonic inflammation (11–13), the nonredundant mechanisms of regulation of intestinal homeostasis or pathogen-specific immunity by TFF2 are currently unclear.

This report demonstrates that TFF2 functions as a regulator of intestinal homeostasis that suppresses *T. gondii*-driven type 1 inflammation. TFF2 suppresses p38 MAPK activation and IL-12p70 release from CD8+ dendritic cells (DC) and limits IL-12/23p40 production from macrophages. Oral inoculation of TFF2−/− mice with *T. gondii* results in the rapid clearance of parasites, preventing the development of infection-induced immunopathology. These data extend the importance of TFF2 from mucosal barrier function to a previously unrecognized role in the suppression of the IL-12/IFN-γ axis that drives host immunity against parasitic protozoa.

**Materials and Methods**

**Mice and *T. gondii* infection model**

Six- to 10-wk-old, sex-matched, wild-type (WT), or TFF2−/− C57BL/6 mice bred in-house were used for all studies. For oral *T. gondii* (ME49 strain) infections, brain cyst homogenates were obtained from chronically infected mice, and cyst suspensions were prepared at the concentrations indicated. Mice were infected by oral gavage with 15–50 cysts using a 21-gauge ball-tipped feeding needle. Weight was monitored daily. Moribund mice (>20% weight loss) were sacrificed according to the Institutional Animal Care and Use Committee at the Cincinnati Children’s Hospital Medical Center.

**Histological staining and immunohistochemistry**

*Toxoplasma* Ag-specific immunohistochemistry on paraffin-embedded tissue was performed with anti-*T. gondii* primary Ab (US Biologicals) as described previously (14). For immunofluorescence, paraffin-embedded tissue sections were immersed in 4% donkey serum (Millipore) for 2 h at room temperature to prevent nonspecific binding of primary Abs. Rabbit anti-CD3 (1:100; DakoCytomation) and 5 μg/ml rat anti-mouse F4/80 or anti-CD11b

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Abbreviations used in this article: BMDM, bone marrow-derived macrophage; DC, dendritic cell; IBD, inflammatory bowel disease; mLN, mesenteric lymph node; STAg, soluble tachyzoite Ag; TER, transepithelial cell resistance; TFF, trefoil factor; TFF2−/−, trefoil factor 2-deficient; WT, wild-type.

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(eBioscience) were applied to tissue sections overnight, washed, and incubated with 1% BSA incubated with Donkey anti-Rat 594 and Donkey anti-Rabbit 488 (Invitrogen) for 2 h for detection of primary Ab. DAPI–Fluormount (Southern Biotechnology Associates) was used for nuclear staining.

**Quantitative RT-PCR**

Total RNA was purified from bone marrow-derived macrophages (BMDM) or DC cultures using TRIzol reagent, according to the manufacturer’s instructions (Invitrogen). cDNA was prepared using the TaqMan cDNA synthesis kit (Roche). Gene expression was measured using the Lightcycler 480, and data were normalized to β-actin. Biopsies of small intestine (duodenum, jejunum, and ileum) were pooled and weighed, and DNA was extracted using the DNeasy blood and tissue extraction kit (Qiagen). Primers used for amplification of the *T. gondii* B1 gene: forward, 5'-CTGGCAAAATACGTTAAGT-3', and reverse, 5'-GTTGACTCGCGA-AAATGAATCC-3', as described previously (15). PCRs were setup in a final volume of 20 μl, using 5 μl total tissue DNA, 1 μl 20 μM forward and reverse primer, and 2× SYBR Green I Master Mix (Roche). RT-PCR analysis was performed on a Light Cycler 480 System (Roche). Relative quantification was performed using standard curve analysis of purified parasite DNA from a defined number of parasites and expressed as the number of parasites per milligram of tissue.

**Flow cytometry**

Mesenteric lymph node (mLN) cells were washed in FACS buffer (HBSS, 1% FCS, and 0.2% sodium azide) and incubated with anti-FeRRI/RII mAb (2.4G2). Lamina propria cells were isolated as described previously (16). Single-cell suspensions were stimulated with PMA/onomycin/GolgiPlug (BD Pharmingen) and stained with allopoxycyanin-F4/80 (clone BM8). FITC–anti-CD11b (clone M1/70) and intracellularly stained with PE–anti–IFN-γ mAbs (eBioscience). Intracellular staining with mAb specific for p38 or p42/44 MAPK (Cell Signaling Technology) was performed according to the manufacturer’s protocol. Acquisition was performed with a BD FACS Calibur and analyzed with FlowJo 7.5.5 software.

**BMDM and splenic DC**

BMDM were grown from the mononuclear fraction of bone marrow cultures for 6 d in M-CSF generated by the CMG cell line as described previously (16). Spleen-derived CD11c cells were obtained after collagenase D digestion, followed by CD11c–MACS beads magnetic separation (cell purity >85% as determined by flow cytometry). Soluble tachyzoite Ag (STag) was generated from RH–strain tachyzoites grown from HS27 fibroblasts. CpG was purchased from a commercial vendor (oligosodeoxynucleotide 1826; Coley Pharmaceutical).

**Ab neutralization**

Rat–anti-mouse IL-12/23/40 (C17.8), rat–anti-mouse IFN-γ (XMG1.2), or rat Ig control Ab (GL13) were purified from culture supernatant using thiophilic agarose chromatography, dialyzed against PBS and sterile filtered through a 0.2-μm filter.

**Evaluation of intestinal permeability**

One-centimeter segments of mucosa were mounted in U2500 Dual Channel Ussing chambers that exposed 0.30 cm² tissue to 10 ml Krebs buffer. Agar–salt bridges and electrodes were used to measure the potential difference. Following a 15-min equilibrium period, Basal short-circuit currents (TER) and permeability to FITC–dextran (2.2 mg/ml: molecular mass, 4.4 kDa; Sigma–Aldrich) were determined as described previously (17).

**Statistical analysis**

Statistical significance was assessed by either two-tailed Student *t* test (two groups) or ANOVA for multiple groups with a post hoc test to determine significance using Prism GraphPad 4.0 software.

**Results**

**TFF2 is necessary to maintain mucosal barrier function within the small intestine and limits baseline production of IL-12/23 p40 from myeloid phagocytes**

Treatment of rodents with recombinant hTFF2 ameliorates mucosal injury and TFF2 deficiency in mice exacerbates *Helicobacter* infection-induced mucosal inflammation (9, 12). However, it was unclear whether TFF2 regulated mucosal barrier function under homeostatic conditions. To address this issue, jejunal tissue segments from naive WT and TFF2−/− mice were mounted on Ussing chambers to evaluate both TER (Ω cm²) (Fig. 1A) and paracellular permeability (basolateral to apical flux of FITC–dextran) (Fig. 1B). Strikingly, jejunal tissue from TFF2−/− mice had significantly less TER and significantly more permeability to FITC–dextran than WT tissues (Fig. 1A, 1B). This indicated that TFF2 served a nonredundant role in the mucosal barrier function within the proximal small intestine of mice.

Given this finding, we postulated that the TFF2 deficiency might have led to a dysregulation of immune cell composition or a baseline increase in intestinal inflammation. Evaluation of jejunal biopsies via H&E staining revealed that TFF2−/− mice had a moderate accumulation of leucocytes within the lamina propria but did not possess signs of overt immunopathology (Fig. 1C). Immunofluorescence staining for F4/80 and CD3+ cell populations was used to indicate the relative abundance of myeloid phagocytes and T lymphocytes, respectively. Results show that TFF2−/− mice had a greater accumulation of both cell populations in the lamina propria, as compared with WT mice (Fig. 1D).

To determine whether cytokine dysregulation accompanied these cell compositional changes, 3-cm segments of jejunum were digested with Liberase and evaluated for intracellular IL-12/23p40 levels within the lamina propria macrophage population (CD11b+/F4/80−). Strikingly, the CD11b−/F4/80− cell population from TFF2−/− mice expressed 4-fold greater levels of IL-12/23p40 than WT (Fig. 1E). IL-12p40 mRNA levels within the jejunum were also higher in TFF2−/− tissues than WT, but there were no differences in the baseline expression for IFN-γ or IL-17A as determined by quantitative RT-PCR (data not shown). Taken together, these results indicated that TFF2 served an essential role in the baseline regulation of small intestinal barrier function and inflammatory cell composition/function within the small intestine at baseline.

**TFF2−/− mice control early parasite dissemination without developing intestinal immunopathology following oral infection with *T. gondii* tissue cysts**

Because there were marked perturbations in TFF2−/− mice at baseline, we sought to determine whether these abnormalities would alter the course of disease caused by an oral infection with *T. gondii*. WT and TFF2−/− mice were orally inoculated with Me49 tissue cysts at varying inoculum doses and monitored for changes in weight as an indicator of disease progression. Oral inoculation with 50 cysts (high dose) caused rapid weight loss in both WT and TFF2−/− strains (Fig. 2A), accompanied by marked infection-induced immunopathology within the liver and intestine (Supplemental Fig. 1). However, infection with 25 cysts (medium dose) or 15 cysts (data not shown) did not cause cachexia or mortality in TFF2−/− mice, whereas WT animals lost >20% of their original weight and experienced 30–40% mortality by 8–9 d postinoculation (Fig. 2B). TFF2−/− mice inoculated with 25 tissue cysts did not develop splenomegaly (Fig. 2C) or intestinal inflammation (Fig. 2D), whereas infected WT mice developed severe transmural ileitis characterized by extensive granulocytic infiltration (Fig. 2C, 2D). Concomitant with reduced intestinal inflammation in TFF2−/− mice, the expression levels of IL-10, a key immunosuppressive cytokine, were significantly higher in the ileal tissue of TFF2−/− mice compared with WT at day 7 postinoculation (Fig. 2E). Furthermore, the marked differences between strains in the susceptibility to infection-induced ileitis prompted experiments to test whether reduced immunopathology in TFF2−/− mice correlated with parasite burden. Tachyzoite-specific PCR revealed that
parasite numbers in the intestine of TFF2−/− mice inoculated with 50 Me49 brain cysts (A) or 25 cysts (B) and monitored for weight change. Data show mean ± SE from four to six mice per group. Experiment was repeated four times. Death indicated by cross (**p < 0.01). (C) Representative photographs of spleens from orally infected WT (top panel) and TFF2−/− mice (bottom panel) at 8 d postinoculation. Original magnification ×40. (D) H&E-stained small intestine from WT (top panel) and TFF2−/− (bottom panel) mice at 8 d postinoculation following oral inoculation from experiment described in (B). Original magnification ×200. (E) IL-10 mRNA transcript levels within the jejunum from naive or T. gondii-infected mice at 7 d postinfection with 25 Me49 cysts. Data show mean ± SE from four to six mice per group. Experiment performed twice with similar results.

Although epithelial cells are considered as the major source of TFF2, monocyte/macrophage lineage cells also express TFF2 mRNA. Thus, it was possible that enhanced host resistance to T. gondii infection in TFF2−/− mice involved dysregulation of myeloid phagocyte function(s). To test whether TFF2 served a direct role in the regulation of proinflammatory and anti-inflammatory cytokine release from DC and macrophages, experiments were conducted with TLR-activating microbial Ags. Splenic DC from naive WT and TFF2−/− mice were isolated by magnetic bead sorting (>85% CD11c+), exposed to STAg, and evaluated for IL-12/23p40 mRNA transcript by quantitative RT-PCR. Strikingly, TFF2−/− DC upregulated IL-12/23p40 mRNA transcripts more rapidly than WT DC at 4 h, although there were no differences between strains by 16 h (Fig. 4A). Increased IL-12/23 p40 message levels were accompanied by higher amounts of IL-12p70 produced from TFF2−/− DC cultures as compared with WT.
DC following exposure to STAg or CpG (Fig. 4B). Profilin, a selective TLR11 agonist, also induced greater amounts of IL-12p70 in TFF2−/− DC cultures than WT (Fig. 4C). CpG, a TLR9 agonist, induced IL-10 production that was significantly higher in TFF2−/− DC cultures as compared with WT (Fig. 4D). Collectively, this demonstrated that cell-intrinsic TFF2 expression as well as exogenous rTFF2 pretreatment antagonizes microbial Ag-induced IL-12–driven type 1 inflammation has a central role in driving host protection against T. gondii in mice. Thus, we addressed whether

and suppressed Escherichia coli LPS-induced IL-12/23p40 expression and cytokine release from BMDM (Fig. 4G). Combined, these data indicate that cell-intrinsic TFF2 expression as well as exogenous rTFF2 pretreatment antagonizes microbial Ag-induced proinflammatory cytokine production from myeloid APCs.

Host immunity in TFF2−/− mice is dependent on the IL-12/IFN-γ axis

IL-12–driven type 1 inflammation has a central role in driving host protection against T. gondii in mice. Thus, we addressed whether

FIGURE 3. TFF2 deficiency results in early control of T. gondii replication following ingestion. (A) T. gondii B1-gene specific PCR was performed on small intestine from mice orally inoculated with 25 Me49 brain cysts. The experiment was performed three times with similar results (*p < 0.05). T. gondii tachyzoite–specific immunohistochemistry was used to detect parasites (dark brown precipitate) within the small intestine of WT and TFF2−/− mice at 5 d postinfection from the experiment described in (A). (B) Original magnification ×100; (C) original magnification ×400. Arrows indicate parasite-infected cells.
enhanced resistance afforded by TFF2 deficiency resulted in a preferential expansion of IFN-γ producing effector lymphocytes (21). Intracellular IFN-γ content within TCRβ⁺CD4⁺ and TCRβ⁺ CD8⁺ populations was determined 24 h following CD3 stimulation (1 μg/ml) of mLN cells at day 5 (data not shown) and day 7 following oral inoculation with 25 Me49 tissue cysts. Consistent with our prediction, TFF2⁻/⁻ animals generated a 5-fold greater percentage of IFN-γ⁺ Th1 cells (Fig. 5A) and 3-fold greater percentage of IFN-γ⁺ CD8 effectors (Fig. 5B) than infected WT animals. Importantly, the baseline production of IFN-γ from these T cell subsets was no different between strains, which lends further support to the hypothesis that TFF2⁻/⁻ APC preferentially induced the expansion of IFN-γ⁺-producing lymphocytes following T. gondii infection.

To determine whether the lack of TFF2 indeed protected mice against T. gondii infection through accelerated IL-12/IFN-γ production during acute infection, we tested whether neutralization of these cytokines prior to infection would abrogate protective immunity. Naive WT and TFF2⁻/⁻ mice were given a single dose of anti–IL-12p40 (1 mg) and anti–IFN-γ (1 mg) neutralizing mAbs 1 d prior to oral inoculation with 25 T. gondii tissue cysts. Results show that TFF2⁻/⁻ mice treated with anti–IL-12p40/anti–IFN-γ mAbs lost >20% of their original body weight by 9 d postinoculation, whereas TFF2⁻/⁻ mice treated with isotype control mAb did not develop T. gondii-induced cachexia (Fig. 5C). As expected, WT mice treated with anti-IL-12p40/anti–IFN-γ mAbs also developed worse disease than isotype control-treated animals (22).

Last, we predicted that the enhanced disease severity in TFF2⁻/⁻ mice correlated with an inability to control parasite dissemination. The gut-draining mLN were probed with specific mAb for T. gondii Ags at day 7 postinoculation in both strains. Although TFF2⁻/⁻ mice given control IgG harbored few parasites, WT mLN contained many tachyzoites (Fig. 5D, 5E). In contrast, administration of anti–IL-12p40/anti–IFN-γ mAbs to TFF2⁻/⁻ mice caused a dramatic increase of parasite numbers in the mLN, similar to WT mAb-treated animals (Fig. 5F, 5G). Similar results were observed following immunostaining of splenic tissues (data not shown). These data support our hypothesis that the canonical type 1 cytokines IL-12 and IFN-γ protected TFF2⁻/⁻ mice against susceptibility to T. gondii infection-induced lethality and immunopathology.

**Discussion**

The mechanisms that regulate mucosal barrier function, tissue repair, and inflammation within the gastrointestinal tract are incompletely understood. In this study, oral inoculation of mice with the human parasite T. gondii was used to demonstrate a novel role for TFF2 (known to promote epithelial restitution) in the negative regulation of infection-induced IL-12 production and type 1 immunity. TFF2 deficiency increased baseline intestinal inflammation and augmented infection-induced type 1 cytokine production from CD8⁺ DC and CD4⁺ and CD8⁺ T lymphocytes. This provided a selective advantage for the TFF2⁻/⁻ strain in the control of early parasite replication, such that infection-induced immunopathology was averted. Interestingly, TFF2 functioned through cell-intrinsic and extrinsic mechanisms to suppress TLR-driven IL-12 production from macrophages and DC, suggesting that homeostatic TFF2 release within the small intestine has multiple functions that maintain mucosal barrier integrity and downmodulate myeloid APC activation and cytokine production in response to microbial Ags.

The proinflammatory cytokine IL-12 drives host immunity against a variety of microbial, fungal, and viral pathogens (5, 21, 23) including rodents infected with T. gondii (24). Unlike human toxoplasmosis, oral inoculation of C57BL/6 strains with T. gondii tissue cysts causes rapid and severe weight loss (cachexia), intestinal immunopathology, and host mortality within 7–12 d (25). Lethal ileitis caused by oral T. gondii infection bears striking similarity to murine and human IBD, because both are due to

![Figure 5](http://www.jimmunol.org/Downloadedfromhttp://www.jimmunol.org/)
excessive IL-12– and IL-23–driven inflammatory responses aggravated by gut microbes (26, 27). One hypothesis for the similarities in phenotypes of IBD and murine toxoplasmosis is that microbial flora enter the intestinal tissue through areas of damaged epithelium (28). Naive TFF2−/− mice had higher baseline levels of IL-12/23p40 in the intestine than WT, which was concurrent with impaired TFR and increased paracellular permeability. These parameters are a central feature of IBD in mice and humans and can be used to indicate the degree of injury to the mucosal barrier within the intestine (29–31). Defective barrier function at baseline in TFF2−/− mice was unexpected, because TFF family members have functionally redundant roles in mucosal epithelial cell repair (32, 33). Although the explanation(s) for this defective barrier function remains undefined, one possibility is that TFF2−/− mice have defective expression/function of gap-junction proteins because of the role of TFF2 in the regulation of cell adhesion molecule expression (34). Alternatively, TFF2 deficiency could result in excess intestinal epithelial cell death because several TFF family members block apoptosis (35, 36). Irrespective of the exact mechanism, our evidence for decreased barrier function in naive TFF2 mice may partially explain why TFF2−/− mice have increased susceptibility to chemical- and infection-induced models of gastritis and colitis (11).

This work demonstrates that TFF2 suppressed IL-12 production in splenic DC and macrophages through extrinsic and intrinsic mechanisms, which demonstrates a previously unrecognized role for TFF2 in the regulation of type 1 inflammation. CD8+CD11c+ DC, a major source of T. gondii infection-induced IL-12p70, produced more IL-12 when isolated from TFF2−/− mice compared with WT. This production was suppressed when WT DC were exposed to exogenous rTFF2. IL-12/23p40 production from intestinal lamina propria macrophages was highly elevated in TFF2−/− mice as compared with WT. This classically activated macrophage phenotype is consistent with reports showing that TFF2−/− mice are hypertresponsive to IL-1β stimulation and that TFF2−/− macrophages show enhanced NF-κB activation compared with WT macrophages (13). In addition, TFF2−/− monocytes release greater amount of reactive nitrogen intermediates and inflammatory cytokines than WT monocytes (11, 13). Because there were no obvious differences between WT and TFF2−/− macrophages or DC in the absence of microbial Ag stimulation, we favor a hypothesis that TFF2 limits Ag-induced activation of myeloid APC.

Our data may suggest that systemic release of TFF2 following tissue injury could antagonize cell-mediated immunity. Indeed, dysregulation of this protein has been documented in a variety of disease contexts. Elevated TFF2 levels are associated with several different types of cancer (35, 37–39) and may predict the stage of tumor progression (40). Furthermore, administration of rTFF2 accelerates the rate of tissue repair in models of burn injury (41), ocular damage (10), gastritis, and colitis (12, 42). In these disease contexts, TFF2-driven suppression of IL-12 production could presumably have a beneficial role in tissue regeneration and the restoration of homeostasis. Taken together, our data show two biological roles for TFF2, which are not mutually exclusive: 1) a negative regulator of IL-12 production from myeloid APC and 2) positive regulator of homeostatic mucosal barrier function. Thus, it is likely that TFF2−/− mice may also develop enhanced systemic inflammation in a variety of disease contexts. A demonstration that TFF2−/− mice were resistant to T. gondii-induced ileitis was unexpected because infection-induced ileitis is largely the result of proinflammatory cytokine production (26, 43). However, TFF2 deficiency only protected mice against a low dose of parasites and succumbed to multorgan inflammation and pathology when inoculated with 50 T. gondii tissue cysts instead of 25 or 15 cysts. Therefore, the selective advantage of TFF2 deficiency is only evident up to a certain threshold of parasite inoculum. Once this is exceeded, the baseline inflammation within TFF2−/− mice is no longer sufficient to limit parasite replication and dissemination throughout the host. This is supported by our demonstration that neutralization of IL-12/IFN-γ prior to infection resulted in uncontrolled tachyzoite replication and cachexia in TFF2−/− mice.

In contrast, anti-inflammatory cytokines such as IL-10 have been demonstrated to serve an essential role in limiting excessive IL-12/IFN-γ–associated immunopathology following T. gondii infection in rodents. Enhanced IL-10 production from infected TFF2−/− mice and TFF2−/− DC could have contributed to suppression of excess immunopathology. However, rTFF2 treatment of DC or macrophages did not induce IL-10 or TGF-β mRNA expression (data not shown). Thus, although the anti-inflammatory effects of TFF2 are unlikely to be IL-10 dependent, the enhanced IL-10 in TFF2−/− mice may have served an important biological role in the context of T. gondii infection. The mechanism(s) responsible for TFF2’s immunosuppressive effects are currently under investigation.

The role of cross-talk between epithelial cells and leukocytes in the regulation of mucosal and systemic immunity has become increasingly apparent. Our data show that TFF2, a major component of mucus, serves an essential role in the negative regulation of IL-12/23p40 and IL-12p70 production from macrophages and DC as well as enforcement of homeostatic mucosal barrier integrity. Taken together, our work is consistent with the emerging concept that epithelial cell repair proteins have direct immunomodulatory functions.

Disclosures

The authors have no financial conflicts of interest.

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