Host Resistance in the Brain against *Toxoplasma gondii*

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Interferon (IFN)-γ-dependent, cell-mediated immunity plays the major role in resistance against development of toxoplastic encephalitis (TE). Humoral immunity also participates in controlling *Toxoplasma gondii* in the brain. Resistance is operative under collaboration among T and B cells, IFN-γ-producing non–T cells, microglia, astrocytes, and dendritic cells. A number of cytokines, including IFN-γ, mediate interactions between these cells and activation of effectors that prevent intracellular replication of the parasite. The *L*4 gene confers resistance against development of TE in mice. In humans, the HLA-DQ1 and -DQ3 genes are involved in regulating the resistance and susceptibility. Since these genes are a part of the major histocompatibility complex, which regulates the immune responses, the regulation of the responses by these genes appears to be important for determining host resistance to this disease. Strains of *T. gondii* also affect development of TE. Genotypes of the parasite may be an important factor for determining development of TE.

*Toxoplasma gondii* is a ubiquitous, obligate intracellular protozoan parasite in humans and animals, and in its latent (cyst) form, it is likely one of the most common infections of humans. In patients with AIDS, *T. gondii* emerged as a major opportunistic pathogen, especially of the central nervous system. Toxoplastic encephalitis (TE) in AIDS patients is almost always due to reactivation of the chronic infection and results from a progressive impairment of immune functions [1, 2]. Reactivation is caused by disruption of tissue cysts followed by proliferation of tachyzoites. TE also occurs in non-AIDS immunocompromised patients. These facts clearly indicate the importance of a normal immune response in resistance of the brain to *T. gondii*. Cell-mediated immunity plays the major role in the resistance to *T. gondii*, although humoral immunity is also involved.

**Cells for Resistance**

* T cells. It is clear that T cells are essential for resistance against *T. gondii* since athymic nude mice, which lack T cells, succumb to the acute infection, and their mortality is associated with proliferation of large numbers of tachyzoites in various organs, including the brain [3, 4]. CD8+ T cells are the major efferent limb of cellular immunity against acute infection, but CD4+ T cells are also involved [5, 6]. The protective activity of CD8+ T cells is predominantly mediated by interferon (IFN)-γ [6, 7], and these cells appear to be a major source of IFN-γ during the acute stage of the infection. However, both CD8+ and CD4+ T cells obtained from the spleen of infected mice can produce this cytokine in vitro following stimulation with tachyzoite antigens [6]. IFN-γ also plays a critical role in prevention of TE during the late stage of infection in mice [8, 9]. My colleagues and I previously reported that neutralization of the activity of IFN-γ in chronically infected mice by treatment with anti–IFN-γ monoclonal antibody (MAb) resulted in severe acute inflammation and development of large areas of necrosis in their brains [8]. In the areas of acute inflammation and necrosis, tachyzoites and *T. gondii* antigens were detected, indicating that such inflammatory responses were caused by proliferation of tachyzoites. Reverse transcription–polymerase chain reaction revealed increased amounts of tachyzoite-specific SAG1 and SAG2 mRNA in the brains of mice following treatment with anti–IFN-γ MAb, reflecting the marked increase in the number of tachyzoites [10]. Thus, it is clear that IFN-γ is critical for preventing proliferation of tachyzoites in the brains of mice. The same appears to be true in humans since the ability of AIDS patients to produce IFN-γ is impaired [11], and they frequently develop TE [1]. Both CD4+ and CD8+ T cells infiltrate the brain of mice following *T. gondii* infection [12–14]. Gazzinelli et al. [9] reported that CD4+ and CD8+ T cells act additively or synergistically to prevent development of TE, probably through their production of IFN-γ. Brown and McLeod [15] reported that CD8+ T cells are involved in the resistance by regulation of the numbers of *T. gondii* cysts in the brains of mice.
In addition to production of IFN-γ, both human and mouse CD4+ and CD8+ T cells can kill *T. gondii*-infected target cells in vitro in a major histocompatibility complex (MHC)-restricted manner [16–20]. Denkers et al. [21] reported an accelerated mortality beginning 75 days after infection in perforin-deficient mice. In their studies, approximately half of the perforin-deficient animals survived until 150 days after infection, but all CD8+ T cell–deficient mice died by 50 days after infection [21]. Thus, perforin-mediated cytolysis by T cells appears to play a limited role in resistance against *T. gondii*. Since perforin-deficient mice die during the late stage of infection, the cytotoxic activity of T cells might play a role in prevention of TE. This point needs clarification. Human and murine T cells specific for *T. gondii* antigens directly lyse extracellular tachyzoites in vitro [18, 22]. The role of such T cell activity in resistance against the infection in vivo is not known.

Bcl-3 oncogene, a distinct member of the Bcl family, which functions as a positive regulator of nuclear factor α (NF-κB) activity, plays a critical role in mounting a protective Th1 immune response to *T. gondii* [23]. Bcl-3–deficient mice survive the early acute stage of the infection; however, most of them die 3–5 weeks after infection. The ability of spleen cells to produce IFN-γ in response to *T. gondii* antigens is normal in the early stage (7 days after infection) but impaired in the later stage (12–31 days after infection). Cytotoxic activity of T cells but not NK cells is also defective in these mice. These results suggest a critical role for Bcl-3 in antigen-specific priming of the long-term, protective Th1–type T cells following infection with *T. gondii*.

Caamano et al. [24] recently showed the importance of NF-κB2 for T cell responses in resistance to TE. NF-κB2–deficient mice have no defect in their ability to produce interleukin (IL)-12 and IFN-γ during the acute stage of infection. However, during the chronic stage of infection, the deficient mice succumbed to TE in association with a reduced production of IFN-γ by splenocytes. Apoptosis of T cells appears to be involved in the reduced production of this cytokine.

**NK cells.** NK cells also have been identified as a major source of IFN-γ in vitro in response to *T. gondii*. IL-12 plays the crucial role for initiating IFN-γ production by NK cells [25, 26], and in collaboration with IL-12, other monokines, such as tumor necrosis factor (TNF)-α, IL-1β, and IL-15, potentiate production of IFN-γ [27, 28]. Hunter et al. [29] recently reported the importance of the CD28/B7 interaction in stimulating IFN-γ synthesis by NK cells. In murine models, IFN-γ production by NK cells is important for controlling *T. gondii* during the early stage of infection [25, 30].

In addition to controlling the parasite, NK cells appear to play a critical role in inducing the protective T cell response. IL-12 is important in the induction of Th1–type T cell development [31]. Scherton-Kersten et al. [32] reported that mice lacking IFN-γ consensus sequence binding protein (ICSBP) are deficient in IL-12 synthesis and are highly susceptible to infection with *T. gondii*. Since ICSBP is normally induced by IFN-γ, these findings suggest that IFN-γ is necessary for optimum production of IL-12 and development of the protective immune response. It is likely that NK cells provide the initial IFN-γ required for optimum IL-12 production during the early stage of the infection. As mentioned earlier, NK cells need IL-12 to produce IFN-γ. Dendritic cells appear to be the source of this IL-12 since it was demonstrated that mouse dendritic cells produce large amounts of IL-12 in response to *T. gondii* in vitro in the absence of IFN-γ [33].

In contrast to the early stage of infection, in the late stage, NK cells do not appear to be crucial for prevention of TE. My colleague and I recently showed that depletion of NK cells did not abolish resistance to development of TE in SCID mice that had received adoptive transfer of immune T cells [34]. In the study, NK cells were undetectable by flow cytometry in the brains and spleens of depleted mice.

**IFN-γ-producing non–T cells.** Adoptive transfer of immune spleen or T cells confers resistance to development of TE in infected athymic nude and SCID mice but not in IFN-γ–deficient mice [34]. Before cell transfer, IFN-γ mRNA was detected in brains of the nude and SCID mice but not in brains of the IFN-γ–deficient mice. IFN-γ mRNA was also detected in brains of infected SCID mice depleted of NK cells, and such animals did not develop TE after receiving immune T cells. Thus, in addition to T cells, IFN-γ production by non-T cells is required for prevention of reactivation of *T. gondii* infection in the brain. The IFN-γ–producing non–T cells do not appear to be NK cells.

**Microglia.** Microglia appear to be major effector cells in the prevention of *T. gondii* tachyzoite proliferation in the brain. Both human [35] and murine [36] microglia become activated in vitro to inhibit intracellular proliferation of tachyzoites following treatment with IFN-γ plus lipopolysaccharide. TNF-α and IL-6 are involved in activation of human microglia [35]. NO mediates the inhibitory effect of activated murine microglia on intracellular replication of tachyzoites: Treatment of these cells with Nω-monomethyl-l-arginine, which blocks the generation of NO, ablates their inhibitory activity [36]. Freund et al. [37] reported an involvement of both NO-dependent and -independent mechanisms in the resistance of murine microglia activated by a combination of IFN-γ and TNF-α. In contrast to these observations in murine microglia, it was reported that NO is not involved in the inhibitory effect of activated human microglia against *T. gondii* [35]. In vivo, following *T. gondii* infection, microglia become activated to produce TNF-α, and IFN-γ mediates the activation [38]. IFN-γ–mediated activation of microglia in collaboration with autocrine TNF-α is likely one of the resistance mechanisms of the brain against *T. gondii*.

CD8+ T cells are important for the regulation of cytokine production, including that of TNF-α, by microglia in *T. gondii*-infected mice [39]. As mentioned in the T cells section above, CD8+ T cells are a major IFN-γ producer during infection. Thus,
CD8+ T cells may be the crucial source of IFN-γ in the brain for activation of microglia to inhibit proliferation of *T. gondii*.

Granulocyte-macrophage colony–stimulating factor (GM-CSF) and transforming growth factor (TGF)-β are other cytokines that appear to be involved in the effector function of microglia. Expression of mRNA for these cytokines increases in the brain following infection [40, 41]. Murine microglia can be activated in vitro to inhibit intracellular multiplication of tachyzoites by treatment with GM-CSF [42] or a combination of IFN-γ and TGF-β [43]. The effect of microglia activated by GM-CSF is due to their synthesis of reactive nitrogen intermediates since their anti–*T. gondii* activity is antagonized by ÑO-monomethyl-L-arginine [42]. In contrast to GM-CSF, macrophage colony–stimulating factor does not activate microglia to inhibit multiplication of tachyzoites [42].

Astrocytes. Astrocytes also appear to inhibit growth of *T. gondii* in the brain. Peterson et al. [44] reported that following treatment with IFN-γ plus IL-1β, human astrocytes are activated to inhibit intracellular proliferation of tachyzoites [44]. This inhibitory effect is mediated by NO [44]. Pelloux et al. [45] reported that TNF-α induced a significant reduction in intracellular multiplication of the parasite in human astrocytoma-derived cells, whereas IL-1α induced an increase in parasite multiplication. TNF-α and IFN-γ were synergistic in activation of indolamine 2,3-dioxygenase (IDO) in human glioblastoma cell lines and native astrocytes [46]. This IDO activity resulted in a strong toxoplasmatic effect mediated by glioblastoma cells activated by treatment with a combination of these cytokines [46].

Murine astrocytes can also inhibit proliferation of tachyzoites in vitro. Halonen et al. [47] reported that pretreatment of murine astrocytes with IFN-γ resulted in 65% inhibition of tachyzoite replication, whereas either TNF-α, IL-1, or IL-6 treatment alone had no effect on replication of the parasite. IFN-γ in combination with TNF-α, IL-1, or IL-6 caused a 75%–80% inhibition of replication [47]. The inhibitory effect of activated murine astrocytes, unlike that of human astrocytes, is not mediated by NO or IDO [47].

Following infection with *T. gondii*, astrocytes become activated to produce IL-1 and IL-6 [48]. These proinflammatory cytokines produced by astrocytes together with those produced by activated microglia likely play an important role in inducing the infiltration of immune cells into the brain.

Dendritic cells. Cells bearing the dendritic cell markers, such as CD11c and 33D1, are located at inflammatory sites in the brain of mice infected chronically with *T. gondii* [49]. These brain dendritic cells are mature as indicated by high-level expression of MHC class II, CD40, CD54, CD80, and CD86, and can trigger antigen-specific T cell responses in vitro. Dendritic cells were the major producers of IL-12 among mononuclear cells isolated from brains of infected animals [49]. GM-CSF is suggested to be important for induction of the dendritic cells in primary brain cell cultures with *T. gondii* [49].

*B cells.* Frenkel and Taylor [50] examined the effect of B cell depletion (accomplished by treatment with anti-μ antibody) on toxoplasmosis in mice infected with a virulent strain and treated with sulfadiazine. After discontinuation of the sulfadiazine treatment, the mice had increased mortality associated with pneumonia, myocarditis, and encephalitis. Administration of antiserum to *T. gondii* reduces mortality in these animals. These results suggest that antibody production by B cells may be important for controlling the latent persistent infection. However, these studies do not provide conclusive information because of the potential side effects of anti-μ antibody treatment on the immune system.

Recently, we examined the role of B cells in resistance to *T. gondii* by using B cell–deficient (μMT) mice generated by disruption of one of the membrane exons of the μ-chain gene [51]. All B cell–deficient mice died between 3 and 4 weeks after infection, whereas no mortality was observed in the control mice until 8 weeks after infection. At the stage during which μMT animals succumbed to the infection, large numbers of tachyzoites were detected only in their brains. Furthermore, treatment of infected μMT mice with anti–*T. gondii* IgG antibody reduced mortality and prolonged the time to death. These results indicate that B cells play an important role, through the production of specific antibodies, in preventing TE in mice.

Cytokines for Resistance

IFN-γ, TNF-α, and inducible NO synthase (iNOS). As mentioned above in the T cells section, IFN-γ is the central cytokine in resistance against *T. gondii* during both the early and late (TE) stages of the infection. Following *T. gondii* infection, macrophages become activated to kill intracellular tachyzoites. This process is mediated by IFN-γ as shown in experiments in which anti–IFN-γ MAb blocked the activation of macrophages [52]. In the absence of activity of endogenous IFN-γ, mice die within 1 week after intraperitoneal infection, and their mortality is associated with numerous tachyzoites in their peritoneal cavities [52]. Thus, IFN-γ–mediated activation of macrophages is critical for resistance against acute infection with this parasite.

Murine peritoneal macrophages become activated after treatment with a combination of IFN-γ and TNF-α in vitro, and the activated cells inhibit intracellular replication of tachyzoites through production of NO by iNOS [53]. However, TNF-α and iNOS are not essential for controlling acute infection in vivo since mice lacking TNF receptor types 1 and 2 (TNF-R1 and -R2, respectively) and those lacking iNOS control parasite growth in the peritoneal cavity following intraperitoneal infection [54–56]. Consistent with these findings are the results of experiments in mice lacking IFN-γ regulatory factor 1 (IRF-1), which is essential for iNOS induction by IFN-γ [57]. Although the IRF-1–deficient animals are more susceptible than control animals to infection with *T. gondii*, they survive the acute stage...
of the infection through iNOS-independent mechanism(s). These results indicate that the protective mechanism(s) that requires IFN-γ but not TNF-α or iNOS is sufficient for mice to control parasite growth during the acute stage of the infection. Candidates for such mechanisms are degradation of tryptophan by IDO [58], release of reactive oxygen intermediates [59], or limitation of the availability of intracellular iron to the parasite [60]. Unrecognized, novel mechanisms may also be involved.

In contrast with TNF-R1/R2− or iNOS-deficient mice in the acute stage of infection, such mice in the late stage of infection succumbed to necrotizing TE [54–56]. These results are consistent with those of earlier studies: Treatments of infected wild-type mice with anti-TNF-α MAb or aminoguanidine, an iNOS inhibitor, resulted in the development of TE [10, 61]. Thus, TNF-α and iNOS are critical for prevention of proliferation of tachyzoites in the brain. As mentioned above, IFN-γ plays the central role in resistance of the brain against this parasite [8, 9]. Since neutralization of IFN-γ or TNF-α results in decreased iNOS expression and development of severe TE [10], activation of iNOS mediated by IFN-γ and TNF-α appears to play a key role in the prevention of TE. Microglia and astrocytes are likely the effector cells involved in this protective mechanism (see Microglia and Astrocytes sections above).

Yap et al. [54] reported that iNOS induction in the brain was not impaired in T. gondii−infected TNF-R1/R2−deficient mice that are susceptible to TE, suggesting that TNF-dependent immune control of T. gondii expansion in the brain involves an effector function distinct from iNOS activation. More recently, Deckert-Schüter et al. [55] reported that mice lacking TNF-R1 but not those lacking TNF-R2 developed necrotizing encephalitis following T. gondii infection and that a remarkable reduction of iNOS synthesis was observed in the brains of TNF-R1−deficient animals compared with TNF-R2−deficient or control animals. They concluded that signaling through TNF-R1 (but not through TNF-R2) provides the stimulus required to induce iNOS activation in the brain following T. gondii infection [55]. Thus, it appears that there are two pathways to activate iNOS in the brain of T. gondii−infected mice: One is TNF dependent and the other TNF independent. Since different strains of T. gondii were used in the studies mentioned above [54–55], the strain of the parasite may be an important factor affecting the activation pathway for iNOS.

Involvement of iNOS-independent mechanisms in the prevention of mortality in T. gondii−infected mice was recently demonstrated in an elegant study by Yap et al. [62] using bone marrow chimeras. Resistance to acute and persistent infection was displayed only by mice in whom IFN-γ receptors and TNF-R1/R2 were expressed in both hematopoietic and nonhematopoietic cells. In contrast, expression of iNOS by only hematopoietic cells was sufficient for host resistance. These results suggest that in concert with bone marrow–derived effector cells, nonhematopoietic cells can directly mediate IFN-γ− and TNF-α−dependent resistance to the parasite. This resistance does not require expression of iNOS in nonhematopoietic cells.

Resistance to development of TE is under genetic control in both humans and mice (see the Host Genes Involved in Resistance section below). My colleagues and I recently obtained evidence suggesting a crucial role of an IFN-γ−dependent, iNOS-independent mechanism in the genetic resistance of BALB/c mice to this disease: BALB/c-background, IFN-γ−deficient mice infected and treated with sulfadiazine developed severe TE after discontinuation of sulfadiazine treatment, although compared with control animals, these animals expressed equivalent amounts of mRNA for TNF-α and iNOS in their brains [63]. These results indicate that expression of TNF-α and iNOS is insufficient for prevention of TE in the absence of IFN-γ.

IL-12. IL-12 is required for the development of IFN-γ−dependent resistance to T. gondii during the acute stage of infection (see the T cells and NK cells sections). However, the role of IL-12 in resistance during the chronic stage of infection was unclear since neutralization of this cytokine did not increase mortality in mice with TE [64]. Yap et al. [65] recently demonstrated the importance of IL-12 for the maintenance of IFN-γ production in T cells mediating resistance to chronic infection. IL-12 p40−deficient mice treated with recombinant IL-12 for the first 2 weeks of infection survived the acute phase and established chronic infections. However, 4–6 weeks after IL-12 withdrawal, the mice exhibited increased brain cyst burdens and succumbed to TE in association with a loss of T cell−dependent IFN-γ production. IL-12 appears to be required for the long-term maintenance of IFN-γ−dependent resistance against T. gondii.

IL-4. CD4+ T cells are known to be heterogeneous (Th1 and Th2) with regard to cytokine secretion. Th1 cells preferentially secrete IL-2 and IFN-γ, whereas Th2 cells preferentially produce IL-4, IL-5, IL-6, and IL-10. IL-4 has been reported to have a dominant effect on determining the pattern of cytokines (Th2-type) produced by CD4+ T cells upon subsequent antigen stimulation in vitro. Since IFN-γ is critical for preventing development of TE (see the IFN-γ, TNF-α, and iNOS section), my colleagues and I examined the role of IL-4 in the pathogenesis of TE, using IL-4−targeted mutant (IL-4−/−) mice [66]. Surprisingly, IL-4 was protective against the development of TE. All IL-4−/− mice died during the late stage (6–20 weeks) of infection, whereas all control mice survived. Histologic study revealed significantly greater numbers of cysts and areas of acute focal inflammation associated with tachyzoites in the brains of IL-4−/− compared with control mice 4–8 weeks after infection [66]. These results indicate that IL-4 is protective against the development of TE by preventing the formation of cysts and proliferation of tachyzoites in the brain.

Eight weeks after infection, spleen cells of control mice produced significantly greater amounts of IFN-γ following stimulation in vitro with soluble T. gondii antigens than spleen cells
of IL-4−/− mice [66]. These results indicate that IL-4 plays a role in enhancing IFN-γ production during the late stage of infection. The impaired ability of IL-4−/− mice to produce IFN-γ likely contributes to their susceptibility for development of severe TE. Noble and Kemeny [67] reported that IL-4 enhances IFN-γ production by T cells that already have been primed (differentiated), whereas it suppresses differentiation of unprimed T cells to IFN-γ–producing cells. During infection with T. gondii, IFN-γ production occurs earlier than IL-4 production [68]. Thus, it appears that IL-4 does not affect differentiation of unprimed T cells to IFN-γ–producing cells following T. gondii infection because of the absence (or very low production) of IL-4 in the early stage of the infection, whereas it enhances IFN-γ production by differentiated T cells in the late stage of the infection.

In contrast to the observations made by my colleagues and me [66], Roberts et al. [69] reported that greater numbers of cysts and more severe histologic changes were observed in the brains of control than IL-4−/− mice in the late stage of infection, although the former mice were more resistant to death during the acute stage. The differences the genetic backgrounds of mice and the strain of T. gondii that were used in these two studies may have contributed to the differences in their outcomes.

In addition to the regulatory effects of IL-4 on IFN-γ production, IL-4 also acts to modify intracellular replication of tachyzoites in murine macrophages [70] and human fibroblast cell lines [71]. More studies are needed to elucidate the role of IL-4 in the immunopathogenesis of toxoplasmosis.

**IL-6.** IL-6 is a multifunctional cytokine that regulates various aspects of the immune response, acute-phase reaction, and hematopoiesis [72], and it acts in the nervous system [73]. IL-6 mRNA is expressed in brains of mice infected with T. gondii [9, 40, 41] and is detected in the cerebrospinal fluid of infected mice [74]. To determine the role of IL-6 in the pathogenesis of TE, we examined the development of TE following infection in IL-6−/− mice. IL-6−/− mice had significantly greater numbers of T. gondii cysts and areas of inflammation associated with tachyzoites in their brains than control mice [12]. These results indicate that IL-6 is protective against development of TE by preventing formation of cysts and proliferation of tachyzoites in brains of infected mice.

As determined by reverse transcription–polymerase chain reaction, the amount of IFN-γ mRNA in the brains of infected IL-6−/− mice was significantly less than the amount in the brains of control mice; however, the amount of IL-10 mRNA was greater in the IL-6−/− than in the control animals [12]. In addition, lymphocyte preparations isolated from brains of infected IL-6−/− mice had significantly lower ratios of γδ T cells and CD4+ αβ T cells but higher ratios of CD8+ αβ T cells than those of infected control mice [12]. Of interest, no differences were detected in the ratios of these T cell subsets in spleens from the IL-6−/− and control animals [12]. Therefore, the protective activity of IL-6 against development of TE appears to be through its ability to stimulate IFN-γ production and induce infiltration and accumulation of different T cell subsets in brains of infected mice. In relation to the protective role of IL-6 against TE, Chao et al. [35] reported that treatment of human fetal microglia with IL-6 inhibits intracellular replication of tachyzoites in vitro.

**Host Genes Involved in Resistance**

Development of TE in mice is regulated by the gene(s) within the D region of the MHC (H-2) [75–77]. Mice with the d haplotype in the D region are resistant to development of TE, and those with the b or k haplotypes are susceptible. Freund et al. [78] found that polymorphisms in the TNF-α gene located in the D region of the H-2 complex correlate with resistance against development of TE and with levels of TNF-α mRNA in brains of infected mice. However, more recent studies using deletion mutant mice [75] and transgenic mice [77] demonstrated that the Ld gene in the D region of the H-2 complex, but not the TNF-α gene, is important for resistance against development of TE. Resistance of mice to development of TE is observed in association with resistance to formation of T. gondii cysts in the brain [75–77]. McLeod et al. [79] reported that although the Ld gene has the primary effect on cyst number in the brain, the Bcg locus on chromosome 1 may also affect it.

In humans, HLA-DQ3 was significantly more frequent in white North American AIDS patients with TE than in the general white population or randomly selected control AIDS patients who had not developed TE [80]. In contrast, the frequency of HLA-DQ1 was lower in TE patients than in healthy controls [80]. Thus, HLA-DQ3 appears to be a genetic marker of susceptibility to development of TE in AIDS patients, and DQ1 appears to be a resistance marker. HLA-DQ3 also appears to be a genetic marker of susceptibility to cerebral toxoplasmosis in the congenitally infected fetus. A significantly higher frequency of DQ3 was observed in infected infants with hydrocephalus than infected infants without hydrocephalus or normal controls [81].

The role of the HLA-DQ3 and -DQ1 genes in regulation of the susceptibility and resistance of the brain to T. gondii infection is supported by results from a transgenic mouse study [81]. Expression of the HLA-DQ1 transgene conferred greater protection against parasite burden and necrosis in brains in mice than did the HLA-DQ3 transgene [81]. Expression of the HLA-B27 and -Cw3 transgenes had no effects on the parasite burden [82]. Since the Ld gene in mice and the HLA-DQ genes in humans are a part of the MHC that regulates immune responses, the regulation of the responses by these genes appears to be important in determining the resistance or susceptibility of the host to development of TE.

**Genetic Factors of T. gondii in Determining Resistance**

The strain of T. gondii has been shown to be an important determining factor for susceptibility to development of TE.
in murine models [83, 84]. When animals were infected with the identical number of cysts of either the ME49, Beverley, or C56 strain of T. gondii, the ME49 strain formed significantly greater numbers of cysts in brains than did the other strains; the numbers of cysts formed did not differ between the Beverley and C56 strains [84]. Following treatment with anti–IFN-γ MAb, mice infected with the ME49 strain developed significantly greater numbers of areas of acute focal inflammation in their brains, compared with mice infected with the other strains [84]. Since the ME49 strain formed the largest number of cysts in the brains and induced the most severe encephalitis, the number of cysts in the brain appears to be an important factor in determining the susceptibility of the host to development of TE.

In addition, following treatment with anti–IFN-γ MAb, mice infected with the Beverley strain developed foci of acute inflammation in their brains, whereas animals infected with the C56 strain did not develop such inflammatory changes [84]. As mentioned above, mice infected with the Beverley or C56 strain had similar numbers of cysts in their brains before they were treated with anti–IFN-γ MAb. Therefore, a factor(s) that is related to the strain of T. gondii but not related to the number of cysts in the brain is also important in determining the susceptibility of the host to development of TE. Strains of T. gondii have been classified into three genotypes, types I, II, and III, on the basis of gene polymorphisms [85]. It is noteworthy that both the ME49 and Beverley strains, which induced severe inflammatory changes in brains of mice following immunosuppressive treatment, belong to the same genotype, type II, whereas the C56 strain, which did not induce such inflammatory changes, belongs to type III [85]. The genotypes of the parasite may be an important factor for determining the susceptibility to development of TE. In this regard, Howe and Sibley [86] reported that while strains of all three genotypes were isolated from humans, there is a predominance of type II strains in human cases of toxoplasmosis. Thus, parasite genotypes may influence development of clinical illness in humans.

**References**


